A CHEMOENZYMATIC SYNTHESIS OF THE TRICYCLIC FRAMEWORK ASSOCIATED WITH THE NOVEL MARINE SESQUITERPENOID 2-ISOCYANOALLOPUPUKEANANE

A thesis submitted for the degree of
Doctor of Philosophy of

The Australian National University

by

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Declaration

I declare that, to the best of my knowledge, the material presented in this thesis represents the result of original work carried out by the author during the period 2005-2009 and has not been presented for examination for any other degree. This thesis is less than 100,000 words in length. Established methodologies have been acknowledged, wherever possible, by citation of the original publications from which they derive.

Christine Elisabet Dietinger
February, 2010

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unfortunately did not live to see the end of it. I thank my uncle, aunt and cousins in Finland who persistently keep in touch.

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Publications and Presentations

The following list details the publications and presentations that have resulted from research performed during the candidature of the Doctor of Philosophy.

Publications

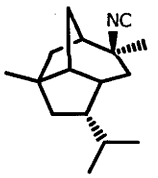
- Dietinger, C. E.; Banwell, M. G.; Garson, M. J.; Willis A. C. *Tetrahedron*, **2010**, submitted

Presentations

- Dietinger, C. E.; Banwell, M. G., A Chemoenzymatic Synthesis of the Tricyclic Framework Associated with the Novel Marine Sesquiterpenoid 2-Isocyanoallopupukeanane.
  Poster presentation at The Royal Australian Chemical Institute NSW Organic Chemistry Group's 30th Annual One Day Symposium;
  Sydney, NSW, Australia, December 2009.

Abstract

The sesquiterpenoid 2-isocyanoallopupukeanane (**14**) was isolated from a nudibranch collected on Hachijo-jima Island in Japan by Fusetani and co-workers in the early 1990's. Its unusual structure and the incorporation of an isonitrile residue within the tricyclic framework have prompted an interest in its biogenesis. As part of a program designed to assist in elucidating the pathway by which the compound is formed *in vivo*, studies directed towards the enantioselective total synthesis of 2-isocyanoallopupukeanane (**14**) have been undertaken and are reported here. The starting material used for this purpose was the *cis*-1,2-dihydrocatechol **59**, a compound that is readily obtained in large quantity and enantiomerically pure form through the whole-cell biotransformation of toluene.



isocyanoallopupu-keanane (**14**)

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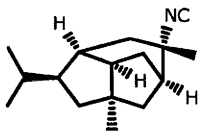
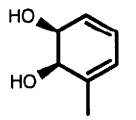
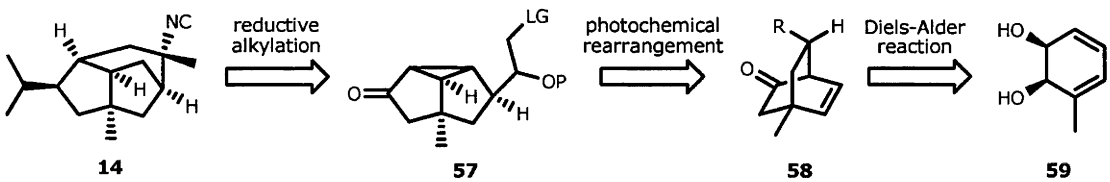


14



59

The present approach to 2-isocyanoallopupukeanane (**14**) involved three key transformations, as shown below in retrosynthetic form. The tricyclic framework of the target, which incorporates a diquinane substructure, was thought likely to be available through an intramolecular alkylation reaction within a diquinane of the general form **57**. An investigation of this process is presented in Chapter 4. Compound **57** itself could be generated *via* a photochemically-promoted oxa-di-π-methane rearrangement of the corresponding bicyclo[2.2.2]octene **58** which proved accessible through an intermolecular Diels-Alder reaction between "toluenediol" **59** and various dienophiles.



14 **57** **58** **59**

Glossary

°C	degrees Celsius
Å	Ångström
Ac	acetyl
4-AcNH-TEMPO	4-acetamido-2,2,6,6-tetramethyl-1-piperidinyloxy, free radical
AD	asymmetric dihydroxylation
AIBN	2,2′-azo-*bis*-isobutyronitrile
$[\alpha]_D$	specific rotation at the sodium D-line
APT	attached proton test (NMR spectroscopy)
aq.	aqueous
atm	atmosphere
Bn	benzyl
BOP	(benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate
Bu	butyl
Bz	benzoyl
c	concentration (g per 100 ml)
ca.	*circa* (approximately)
Celite™	filtration aid consisting of diatomaceous earth
cm	centimetre(s)
conc.	concentrated
d	doublet
δ	chemical shift (parts per million)
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene

DCC	N,N'-dicyclohexylcarbodiimide
deg	degree
$(DHQ)_2PYR$	hydroquinine 2,5-diphenyl-4,6-pyrimidinediyl diether
DIBAL	diisobutylaluminum hydride
DIPEA	diisopropylethylamine
dm	decimetre(s)
DMAP	4-(*N,N*-dimethylamino)pyridine
DMF	*N,N*-dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidone
DMSO	dimethyl sulfoxide
DOWEX™	an ion exchange resin
DPPA	diphenylphosphoryl azide
dppp	1,4-*bis*(diphenylphosphino)propane
E	*entgegen* (opposite)
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
EI	electron impact (mass spectrometry)
ent	a prefix used to indicate the enantiomer of a compound
eq.	equivalents
epi	a prefix used to indicate the epimer of a compound
ESI	electrospray ionisation
Et	ethyl
et al.	*et alia* (and others)
eV	electron volt(s)
EWG	electron-withdrawing group
FGIs	functional group interconversions
FPP	farnesyl pyrophosphate
g	gram(s)
GC-MS	gas chromatography mass spectrum
gCOSY	gradient ^1H-^1H correlated spectroscopy

gHMBC	Heteronuclear Multiple Bond Connectivity (gradient long-range ^{1}H-^{13}C correlated spectra)
gHSQC	Heteronuclear Single Quantum Coherence (^{1}H-^{13}C correlated spectra)
h	hour(s)
hν	irradiation with light
HOBt	1-hydroxybenzotriazole
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
HREIMS	high resolution electron impact mass spectrum
HRESMS	high resolution electrospray mass spectrum
Hz	Hertz
IBX	2-iodoxybenzoic acid
IMDA	intramolecular Diels-Alder
in situ	"in the reaction mixture" (used for compounds/reagents that cannot be isolated and are reacted further in a one-pot reaction)
inter alia	among other things
in vivo	"within the living", inside a living organism
IR	infrared
J	coupling constant (Hz)
kbar	kilobar
l	length
LAH	lithium aluminum hydride
LC50	lethal concentration, 50% (the concentration of a chemical that kills 50% of the test animals in a given time)
LDA	lithium diisopropylamide
LG	leaving group
LiHMDS	lithium *bis*(trimethylsilyl)amide
L-selectride	lithium tri-*sec*-butylborohydride
LUMO	lowest unoccupied molecular orbital
M	molar concentration (mol per litre)
m	multiplet

$M^{+\cdot}$	molecular ion
Me	methyl
mg	milligram(s)
µg	microgram(s)
MHz	mega-Hertz
ml	millilitre(s)
µl	microlitre(s)
mm	millimetre(s)
µm	micrometre(s)
mmol	millimole(s)
µm	micromole(s)
mol	mole(s)
MOM	methoxymethyl
m.p.	melting point (°C)
MS	mass spectrometry or molecular sieves
Ms	methanesulfonyl (mesyl)
m/z	mass-to-charge ratio
n	normal (e.g. unbranched alkyl chain)
NaHMDS	sodium *bis*(trimethylsilyl)amide
nm	nanometre(s)
ν_{max}	infrared absorption maxima (cm^{-1})
NMO	*N*-methylmorpholine oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser enhancement
n. sp.	nova species
Nu	nucleophile
OP	hydroxyl protecting group
ORTEP	Oak Ridge Thermal Ellipsoid Plot
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate

Ph	phenyl
pH	logarithm of the reciprocal of the hydrogen ion concentration, i.e. $-\log_{10}[H^+]$
q	quartet
R_f	retention factor (in chromatography)
s	singlet
sp.	*species*
T	temperature (°C)
t	triplet (when superscript: tertiary)
tert	tertiary
TBAF	tetra-*n*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
tfa	trifluoroacetate
TfO	trifluoromethanesulfonate (triflate)
THF	tetrahydrofuran
TLC	thin layer chromatography
™	trademark
TMEDA	N,N,N′,N′-tetramethylethylenediamine
TPAP	tetra-*n*-propylammonium perruthenate
(*p*-)Ts	*para*-toluenesulfonyl or tosyl
p-TsOH	*para*-toluenesulfonic acid
UV	ultraviolet
vide infra	see below
viz.	*videlicit* (that is, namely)
vs.	*versus*
v/v	unit volume per unit volume (ratio)
W	Watt(s)
Z	zusammen

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Chapter 2: First key-step – Diels-Alder reactions

Chapter 1
Introduction

1.1 Introduction

Natural products belong to a broad class of compounds that are composed of secondary metabolites found in living organisms. Since the beginning of time humans have found use for natural products derived from both the plant and animal kingdoms for purposes as varied as medical treatments, dietary supplements, dyes and perfumes. Traditionally the sources of such compounds have been terrestrial organisms because, until recently at least, their marine counterparts have been largely inaccessible. Only with the arrival of modern scuba diving gear in the 1960's could comprehensive exploration of marine natural products begin.[1]

Since 1965 over 19,000 new marine natural products have been identified. The majority of such compounds are derived from sponges or their symbionts.[2] Sponges are sessile, soft-bodied invertebrates that often accumulate secondary metabolites as part of their defence mechanisms, thereby guarding themselves against the settlement of undesired microbes (fouling) and competing organisms, while, at the same time, fending off predators. Sponge chemicals, as with others derived from marine sources, often incorporate novel structures that have no counterparts in compounds derived from terrestrial species and possess functionalities, such as the often encountered N_1-C_1 moiety, that are rare or entirely absent in non-marine natural products. Prominent examples of such sponge metabolites are the isocyano-substituted terpene class of compounds to which over 150 structures, mostly sesquiterpenes and diterpenes, have been assigned.[3]

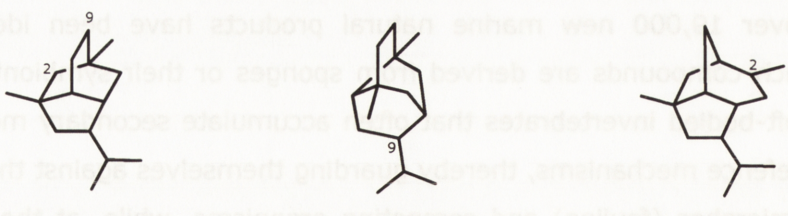
Beside their presence in sponges, isocyano-substituted terpenes have also been detected in nudibranchs. Although some nudibranchs acquire their secondary metabolites through *de novo* biosynthesis,[4] most of them obtain the chemicals by ingestion of sponge tissue[5,6] and may then use these ingested compounds as part of their defense mechanism against predators.[7-9]

1.2 Pupukeananes

Image 1.1. *Phyllidia varicosa*

Pupukeananes are marine sesquiterpenes found in sponges and nudibranchs, which usually carry an N_1-C_1 substituent. The first member of this class, 9-isocyanopupukeanane, was isolated from the nudibranch *Phyllidia varicosa* (Image 1.1*) and its prey - the sponge *Hymeniacidon* sp.[6] Both organisms were collected at the Pupukea site in Hawaii, hence the name of this new class of compound.

The isocyanopupukeananes carry the isonitrile group on C2 or C9 of the carbon skeleton as shown in Figure 1.1. Three "types" of isocyanopupukeananes are now known and distinguished from each other through subtle differences in their skeleta. They are the pupukeananes, neopupukeananes and allopupukeananes, the structural features of which are shown in Figure 1.1.



pupukeanane (**1**) neopupukeanane (**2**) allopupukeanane (**3**)

Figure 1.1. *The pupukeanane (left) and isomeric frameworks*

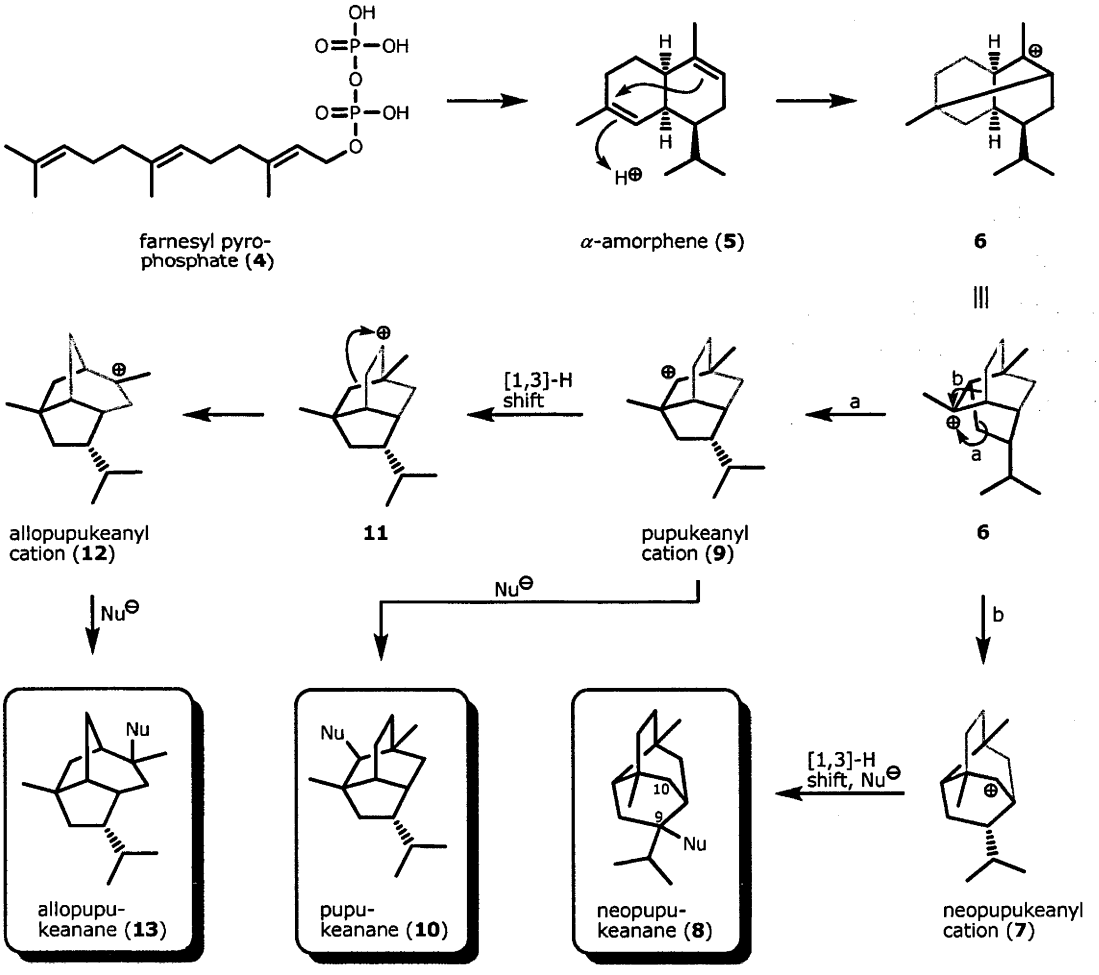
Farnesyl pyrophosphate (FPP, **4**) has been proposed as the common biogenetic precursor to all three skeleta (Scheme 1.1).[10] It is believed that an enzymatically catalysed cyclisation of this precursor, or its isomer nerolidyl pyrophosphate (NPP),

* Available from http://www.sulawesiseaslugs.com/images/nudibranchs/phyllidia_varicosa_05.jpg

followed by a series of acid-catalysed rearrangement steps, leads to the formation of the cadinane type sesquiterpene α-amorphene (**5**).[11] The sequence continues with ring-formation within the latter leading to the cationic twistane species **6**.[10,12] Migration of one of two different bonds (*via* pathway a or b) towards the tertiary cationic centre on this species then gives rise to either a neopupukeanyl cation (**7**) or a pupukeanyl cation (**9**). Rearrangement of the latter through a [1,3]-hydride shift followed by another C-C bond migration then delivers an allopupukeanyl cation (**12**). Trapping of any one of the three different carbocations just mentioned by a nucleophile finally furnishes the relevant neutral (isolated) natural product.†

The remaining discussions are focused on the allopupukeanane group of compounds, to which the chosen target natural product, 2-isocyanoallopupukeanane, belongs.

Scheme 1.1. *Biosynthetic origins of the pupukeananes*



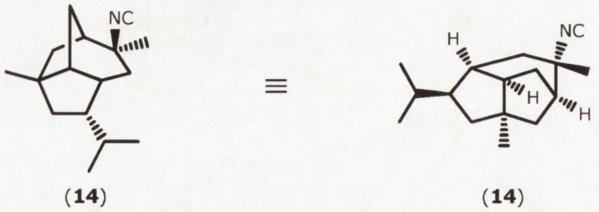
† A C10 substituted neopupukeanane has thus far not been observed. The only reported isocyanoneopupukeanane (Karuso, P.; Poiner, A.; Scheuer, P. J. *J. Org. Chem.* **1989**, *54*, 2095) carries the isonitrile group at C9. A [1,3]-hydride shift from C10 to C9 within carbocation **7** followed by trapping of a nucleophile at C9 could deliver a compound with the general structure **8**.

1.3 2-Isocyanoallopupukeanane

Marine sponge chemicals that carry an N_1-C_1 functionality show interesting biological properties, especially the inhibition of larval settlement. Exploitation of such features could lead to the development of naturally-derived antifouling agents.[13] However, the lack of access to useful quantities of 2-isocyanoallopupukeanane has meant that little is known about the antifouling and other properties of this compound.

2-Isocyanoallopupukeanane (**14**) (Figure 1.2) was originally isolated from the nudibranch *Phyllidiella pustulosa* (Image 1.2[‡]) collected in Japan,[14] and one study has shown that it is ichthyotoxic (LC_{50}= 10μg/ml) towards the killifish *Oryzias latipes*.[14] Structural elucidation of the isolated natural product was accomplished by conventional spectroscopic methods. Due to its gumlike consistency, an X-ray analysis of this material was clearly not possible.[14] Figure 1.2 shows the final assignment of the absolute stereochemistry of the naturally-occurring isomer **14**, which is dextrorotatory. After elucidation of the carbon skeleton of the natural product by 1- and 2-D NMR spectroscopy, the relative configuration of the molecule was established through NOESY experiments.[§]

Image 1.2. *Phyllidiella pustulosa*



(**14**) (**14**)

Figure 1.2. *The structure, including absolute stereochemistry, of 2-isocyanoallopupukeanane (**14**)*

[‡] Available from http://www.seaslugforum.net/find/16433

[§] The absolute stereochemistry of 2-isocyanoallopupukeanane has not been determined although it is presumed to be as illustrated because of its likely biogenetic relationship to 9-isocyanopupukeanane for which the absolute configuration has been established (Hagadone, M. R.; Burreson, B. J.; Scheuer, P. J.; Finer, J. S.; Clardy, J. *Helv. Chim. Acta* **1979**, *62*, 2484)

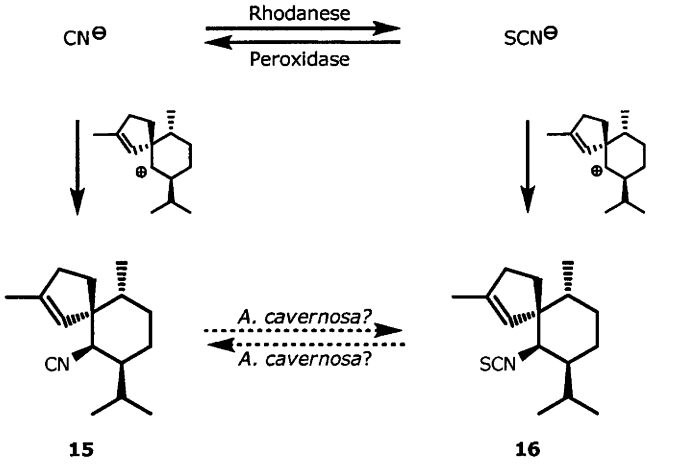
1.4 The origin of the isonitrile group

The origin of the isonitrile group in marine isocyano sesquiterpenes has been under investigation for some time. Incorporation studies using [^{13}C]-labelled 2-isocyano-pupukeanane suggest that the isocyano functionality is not derived from formamide or isothiocyanate precursors.[15] In fact, the opposite is probably the case, *viz.* the formamide and isothiocyanate residues are derived from an isonitrile-containing precursor.

A subsequent study revealed that inorganic cyanide is responsible for the generation of many, if not all, isocyano terpenes.[16] Thus, the feeding of marine sponges of the *Amphimedon* genus with sodium [^{14}C]cyanide resulted in the incorporation of two labelled isonitrile groups into the terpenoid metabolite diisocyanoadociane. Subsequently, and through injection of sodium [^{14}C]cyanide into a *Ciocalypta* sp sponge, Scheuer *et al* were able to isolate labelled 2-isocyanopupukeanane.[17] This same group also showed, by feeding *Ciocalypta* sp with potassium [^{13}C,^{15}N]cyanide, that the nitrogen of the isonitrile group in 9-isocyano-neopupukeanane is derived from inorganic cyanide. The nature of the cyanide incorporation was also explored. Thus, solutions containing pure 2-isocyanopupukeanane or *Ciocalypta* sp hydrocarbons were stirred separately with [^{14}C]cyanide. The faint radioactivity that was observed within the subsequently isolated organic materials suggests that the incorporation of cyanide is an enzyme-mediated process.

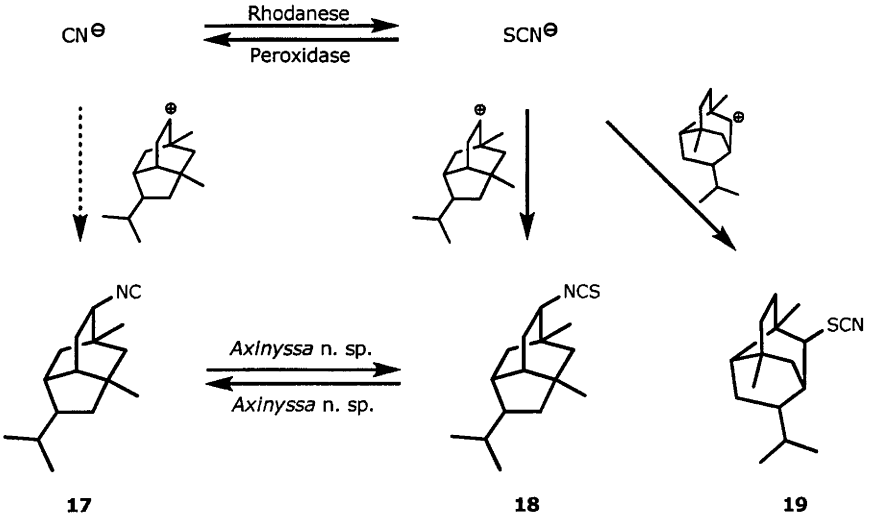
In related studies,[5] a range of incubation experiments was carried out with the sponge *Acanthella cavernosa*, from which the sesquiterpenes axisonitrile-3 (**15**) and axisothiocyanate-3 (**16**) were isolated. It was found that when the sponge was fed with either inorganic [^{14}C]cyanide or [^{14}C]thiocyanate, both of the isolated terpenes **15** and **16** were radioactive. This result suggests that the sponge can incorporate either of these anionic species into the terpene metabolite and that cyanide and thiocyanate are interconverted at the inorganic level (Scheme 1.2).[5] The transformation of cyanide into thiocyanate could be promoted by an enzyme such as rhodanese that is present in many organisms although it has not yet been found in marine sponges.[18] The reverse reaction can be catalysed by certain peroxidases such as lactoperoxidase.[19] Alternatively, an interconversion between isocyanides and isothiocyanates could occur at the secondary metabolite level. Advanced precursor studies would be necessary to confirm that such a transformation is operational, but these could not be carried out with *A. cavernosa* due to the steric congestion at the isocyano/isothiocyanato sites.

Scheme 1.2. *Biosynthetic interconversion scheme for metabolites* ***15*** *and* ***16*** *found in* Acanthella cavernosa



Other work was carried out with the sponge *Axinyssa* n. sp. that produces, *inter alia*, 9-isocyanopupukeanane (**17**), 9-isothiocyanatopupukeanane (**18**) and 2-thiocyanatoneopupukeanane (**19**) (Scheme 1.3).[20] Thus, incubation of this sponge with either [^{14}C]cyanide or [^{14}C]thiocyanate gave unlabelled isonitrile **17** and radioactive metabolites **18** and **19**. These results imply that inorganic cyanide does, indeed, appear to be converted into inorganic thiocyanate and this process is then followed by incorporation of the latter into the isothiocyanato- and thiocyanato-containing metabolites. However, in contrast with the above-mentioned study involving *A. cavernosa*, no incorporation into the isocyano metabolic product could be detected. Following this observation, advanced precursor studies were carried out in *Axinyssa*

Scheme 1.3. *Biosynthetic interconversion scheme for* Axinyssa *n.sp.*



n. sp.[21] Specifically, [^{14}C]-labelled isonitrile **17** and isothiocyanate **18** were prepared *via* semi-synthesis and then separately fed to the sponge. Upon extraction of the sponge, both metabolites had acquired radioactivity in each case. These results indicate that the two metabolites are interconversible but it was also noted that the rate of conversion of isocyanide into isothiocyanate is faster than the reverse process. Overall, then, it is thought that the major biosynthetic route in *Axinyssa* n.sp. starts with the conversion of inorganic cyanide into thiocyanate, followed by incorporation of the latter into an isothiocyanate- or thiocyanate-containing metabolite. The isothiocyanate can be further transformed into the corresponding isocyano-substituted terpene.

So, as matters currently stand, a great deal of effort has been invested in unravelling biological transformations in the sponges *A. cavernosa* and *Axinyssa* n. sp. However, the origin of the inorganic cyanide and thiocyanate remains unclear. Furthermore, additional work has to be done to gather a yet larger amount of data for different kinds of sponges and substrates, including those involving N_1-C_1 based functionalities other than already presented here.

Accordingly, the objective of the work described in the body of this thesis was to establish a synthetic route to compounds incorporating the allopupukeanane framework that could be used in feeding experiments. If a suitable synthetic route to the target 2-isocyanoallopupukeanane could be found then related compounds carrying other N_1-C_1 functionalities, such as isothiocyanato and formamide groups, could be prepared and characterised. Labelling of the resulting adducts would furnish substrates for studies on the biogenesis of these systems.

On this basis, the next Section contains a short overview of published synthetic approaches to 2-isocyanoallopupukeanane. This is followed by a Section detailing the retrosynthetic plan that informed the work described in the remaining Chapters of this thesis.

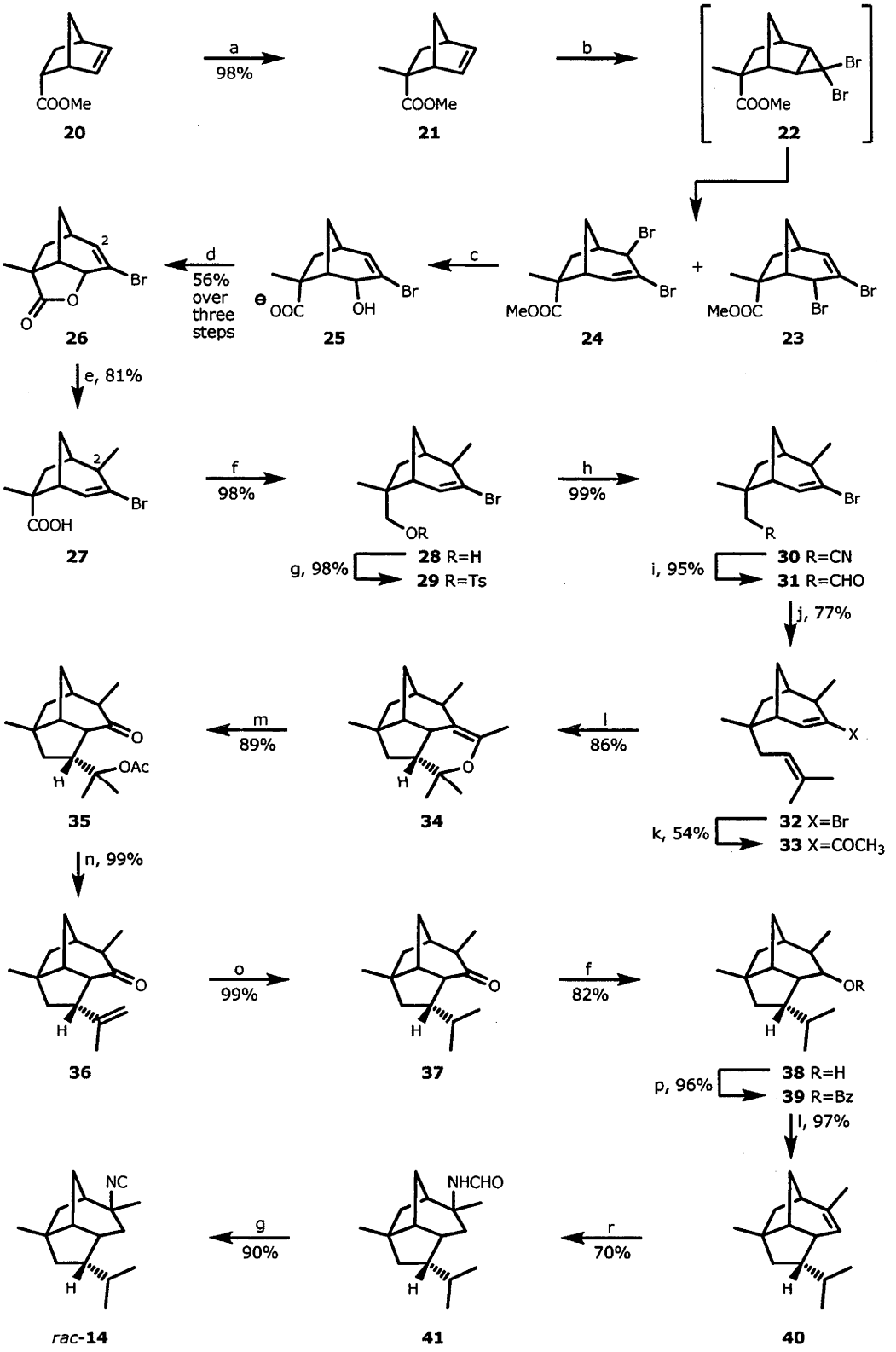
1.5 Previous synthetic studies

Almost two decades have passed since 2-isocyanoallopupukeanane was first isolated.[14] Thus far, however, only one synthesis of the natural product has been completed and this provided the compound in racemic form. Section 1.5.1 gives an overview of how this synthesis was achieved. In the following Section (1.5.2) the key aspects of a more recent publication on the enantioselective assembly of the allopupukeanane framework is described.

1.5.1 The Ho synthesis of (±)-2-isocyanoallopupukeanane

The first and thus far only total synthesis of 2-isocyanoallopupukeanane, which was obtained in racemic form, was carried out by Ho and co-workers (Scheme 1.4).[22] It starts with Diels-Alder adduct **20** obtained *via* the *endo*-selective cycloaddition of cyclopentadiene and methyl acrylate. The α-anion of ester **20** was treated with methyl iodide, a reaction that gave predominantly the illustrated C-alkylated species **21**.[23] The bicyclo[3.2.1]octane moiety of the natural product was then established through a dibromocarbene-promoted ring-expansion of the norbornene framework of adduct **21**. The allylic bromides **23** and **24** so-formed participated in a lactone formation/hydrolysis sequence[24] under basic conditions and finally yielded hydroxycarboxylate **25**. Acidification of the latter caused lactonisation and compound **26** was isolated as the end-product of the sequence. Methylation at C2 then opened the lactone ring via an S_N2' reaction, and the carboxylic acid group thus formed was converted, over a number of steps, into an olefinic side-chain seen in compound **32**. Substitution of the bromine by an acetyl group then furnished species **33** that was subjected to an intramolecular hetero-Diels-Alder reaction to establish the third ring of the tricyclic framework and, simultaneously, a six-membered heterocyclic ring. Cleavage of the double bond within the heterocyclic ring of adduct **34** through ozonolysis then revealed a precursor to the isopropyl group. After several more functional group interconversions, (±)-2-isocyanoallopupukeanane was obtained in 18 steps and 6% overall yield, starting from Diels-Alder adduct **20**.

Scheme 1.4. *The Ho synthesis of (±)-2-isocyanoallopupukeanane*

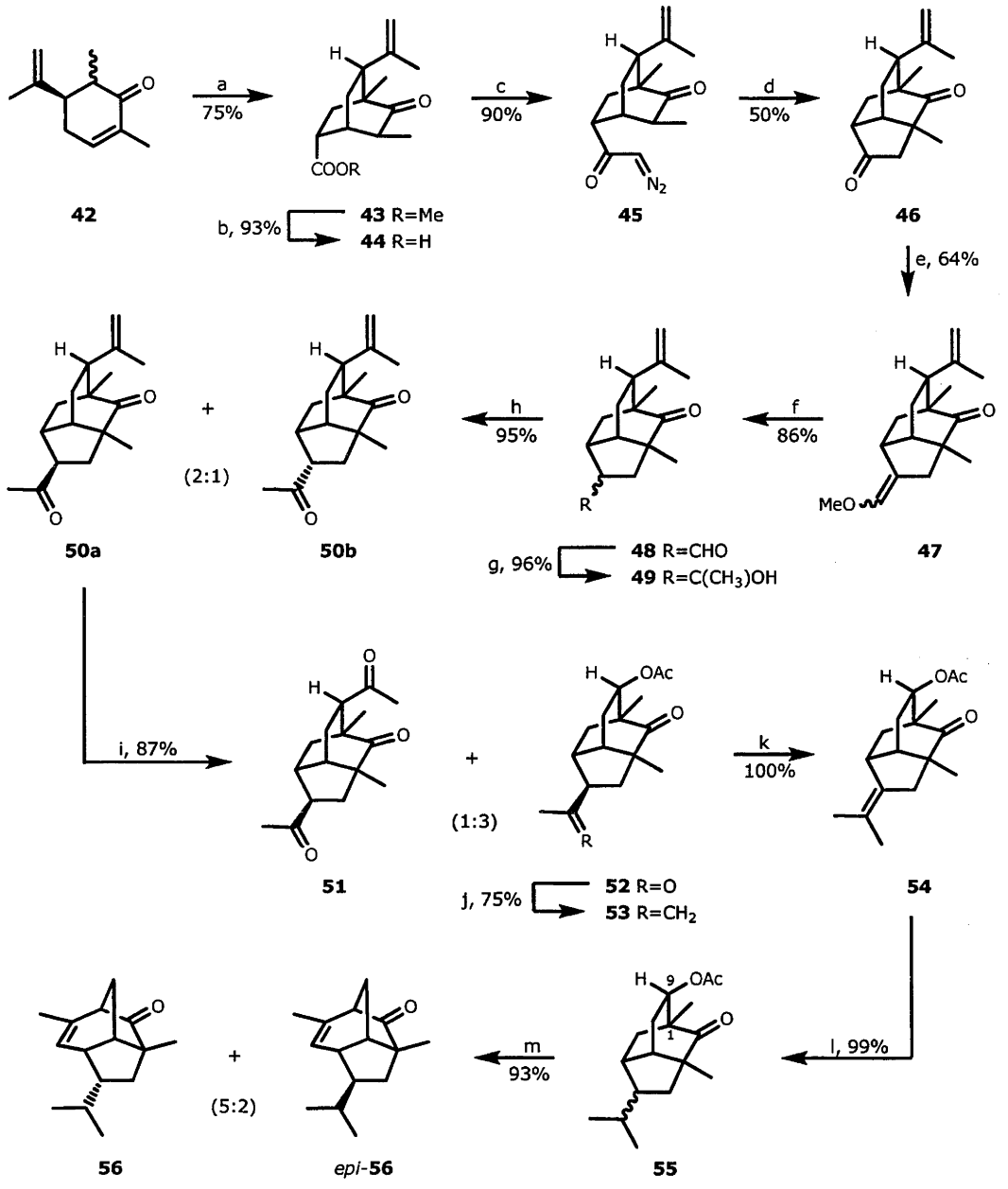


Reagents and conditions: (a) i. LDA, hexane, THF, -78°C, 1h; ii. **20**, MeI, -78°C, 2h; (b) $CHBr_3$-KOH, Bu_3N, benzene, 18°C, 4 days; (c) 10% KOH, THF, 80°C, 12 h; (d) 6 M HCl (e) MeMgI, CuI, Me_2S, THF, ether, -40°C→-10°C, 10 h; (f) $LiAlH_4$, THF, 70°C, 16 h; (g) TsCl, pyridine, 18°C, 16 h; (h) NaCN, DMF, 120°C, 10 h; (i) DIBAL, toluene, hexane, -78°C→18°C, 3 h; (j) $Ph_3P{=}CMe_2$, THF, hexane, 0°C, 4 h; (k) i. *t*-BuLi, THF, pentane, -78°C, 0.67 h; ii. AcN(OMe)Me, -78°C, 1 h; (l) toluene, 225°C, 2 days; (m) O_3, CH_2Cl_2, Me_2S, -78°C→18°C, 12 h; (n) toluene, 410°C; (o) H_2, PtO_2, MeOH, 0°C, 3 h; (p) BzCl, pyridine, CH_2Cl_2, 0°C→18°C, 16 h; (r) NaCN, H_2SO_4, HOAc, 0°C→18°C, 24 h.

1.5.2 Srikrishna's enantioselective synthesis of the *ent*-allopupukeanane skeleton

Srikrishna and his co-worker devised what they claimed to be a biomimetic synthesis of the non-natural enantiomeric form of the framework of allopupukeanone **56** (Scheme 1.5).[25] First, the pupukeanane framework was assembled in 12 steps from 6-methylcarvone (**42**). On this route, the bicyclo-[2.2.2]octane moiety of the pupukeanane skeleton was established through two consecutive Michael addition reactions between compound **42** and methyl acrylate. This furnished compound **43** as the major product. The five-membered ring of the target compound was installed through a rhodium-mediated carbenoid C-H insertion reaction of diazoketone **45**, a process that led to the tricyclic species **46**. The isopropenyl group was transformed into an acetoxy group through a Criegee rearrangement, leading to diketone **52** as the major product. This was of importance for the final step, wherein pupukeanone **55** was converted into allopupukeanone species **56** *via* a pivotal and acid-induced rearrangement that mimics the biological transformation shown in Scheme 1.1 (see isomerisation **11**→**12**). Thus, loss of the elements of acetic acid from the conjugate acid of adduct **55** generated a carbocationic species at C9 that induced a [1,2]-alkyl shift from C1 to C9. In the process a secondary carbocation was transformed into a more stable tertiary isomer (compare Scheme 1.1). Finally, loss of a proton from the rearranged cation gave the allopupukeanone adduct **56**.

Scheme 1.5. *The Srikrishna synthesis of* ent-*allopupukea-2-en-10-one (**56**)*

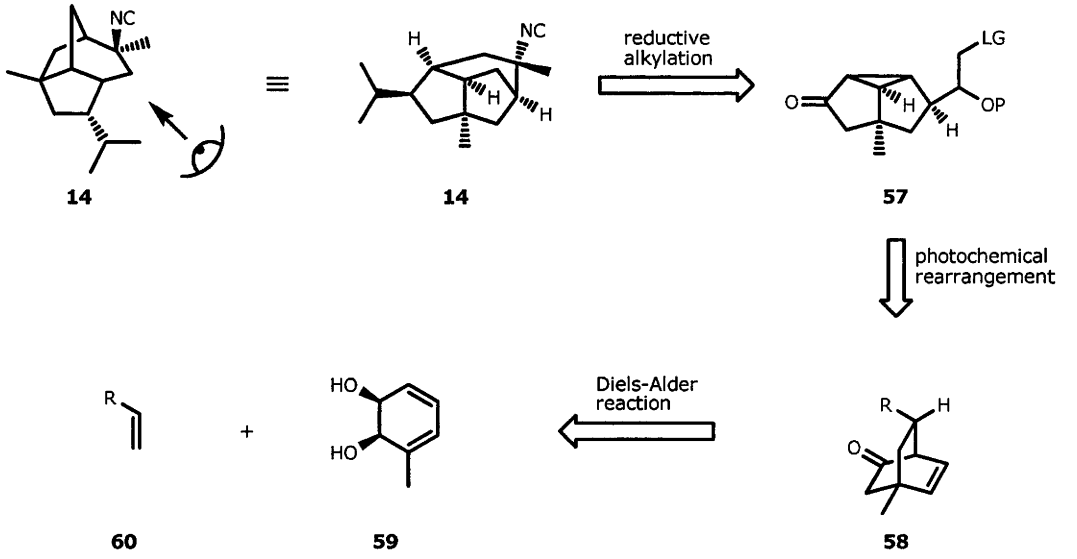


Reagents and conditions: (a) LiHMDS, hexane, H_2C=CHCOOMe, -10°C→18°C, 3 h; (b) NaOH, MeOH, 65°C, 8 h; (c) i. $(COCl)_2$, C_6H_6, 18°C, 2 h; ii. CH_2N_2, Et_2O, 0°C→18°C, 3 h; (d) $Rh_2(tfa)_4$, CH_2Cl_2, 40°C, 4 h (e) Ph_3P=CHOMe, THF, 66°C, 3 h; (f) 3 M HCl, THF, 18°C, 1 h; (g) MeMgI, Et_2O, 0°C→18°C, 0.5 h; (h) PCC, silica gel, CH_2Cl_2, 18°C, 3 h; (i) i. O_3/O_2, CH_2Cl_2, MeOH, -70°C; ii. Ac_2O, Et_3N, C_6H_6, 80°C, 5 h; (j) Ph_3P=CH_2, C_6H_6, 18°C, 0.5 h; (k) $RhCl_3 \cdot nH_2O$, EtOH, 80°C, 24 h; (l) H_2, PtO_2, EtOH, 1 atm, 48 h; (m) *p*-TsOH·H_2O, C_6H_6, 80°C, 3 h;

1.6 Retrosynthetic analysis

The work outlined in this thesis adopts a quite distinct approach to 2-isocyano-allopupukeanane. The relevant retrosynthetic overview starting from the target natural product **14** is provided in Scheme 1.6. By reorientating the target molecule to the perspective shown on the right, it becomes more obvious that the carbon skeleton of target **14** incorporates a diquinane substructure. The plan was, therefore, to construct a diquinane incorporating a carbonyl-conjugated cyclopropane of the general structure **57**. The enolate formed upon reductive cleavage of the cyclopropane ring would be expected to participate in an intramolecular alkylation reaction with a pendant electrophile so as to form a six-membered ring and thereby establish the target framework. Functional group interchanges on the thus obtained adduct would complete the synthesis of target **14**. Subjection of a bicyclo[2.2.2]octene of the general structure **58** to an oxa-di-π-methane rearrangement was expected to deliver the required diquinane-containing compound.[26] The bicyclic photochemistry precursor **58** was, in turn, considered likely to be accessible through a Diels-Alder reaction between the enantiomerically pure *cis*-1,2-dihydrocatechol **59** and a dienophile such as **60**. This proposed retrosynthetic analysis of the target compound is discussed in more detail in the following Sections. Two routes were considered, one leading to the natural enantiomer of the target (Section 1.6.1) and the other providing the non-natural enantiomeric form of 2-isocyanoallopupukeanane (Section 1.6.2).

Scheme 1.6. *Retrosynthetic overview*

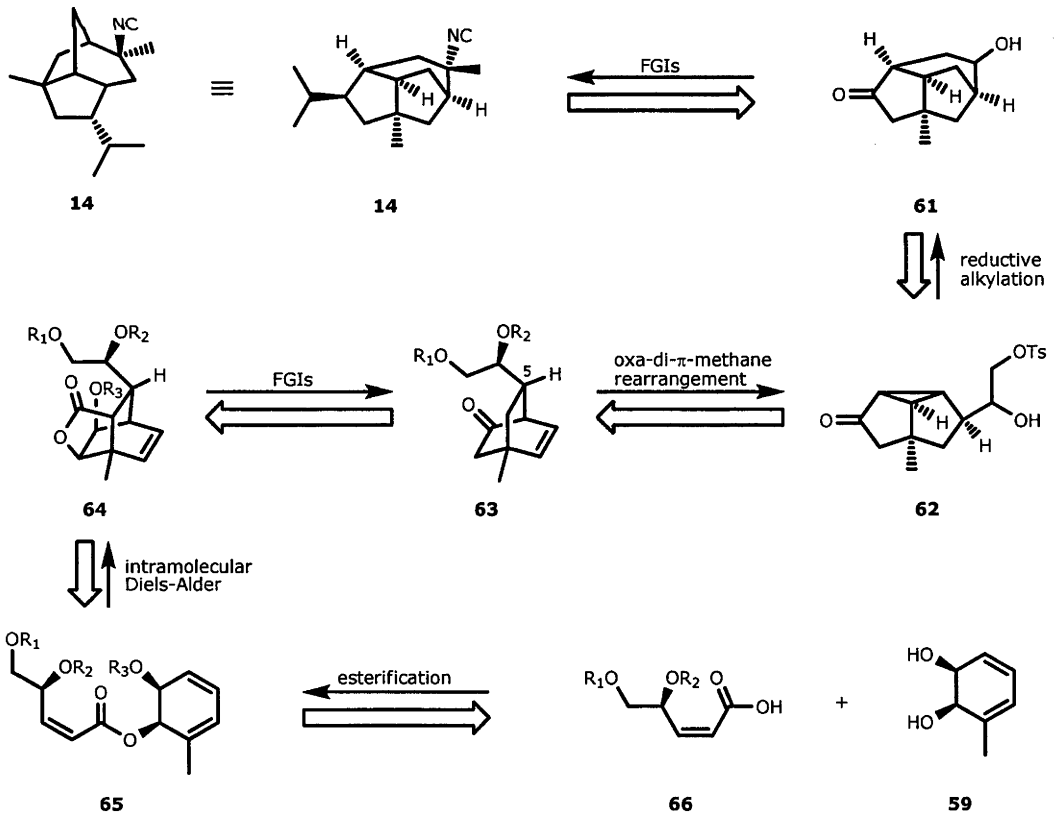


LG...leaving group, R...two-carbon side-chain with LG, P...hydroxyl protecting group

1.6.1 A strategy towards the natural enantiomer of the target compound

Scheme 1.7 depicts the originally devised retrosynthetic analysis of the natural enantiomeric form of 2-isocyanoallopupukeanane (**14**). As mentioned in the preceding Section, the plan was to gain access to the complete carbon skeleton of the natural product through an intramolecular alkylation within a diquinane species that would thereby establish the six-membered ring of the target. Thus, diquinane **62** is "bowl-shaped" due to the *cis*-fusion of the two five-membered rings. The proposed reductive alkylation step is only possible when the pendant side-chain is in an *endo*-orientation and so directed towards the inside of the bowl. The latter requirement, in turn, demands the illustrated configuration of the substituents at C5 on the ethano bridge of the bicyclic precursor **63** to diquinane **62**. Moreover, the bicyclic adduct needs a keto group and a double bond in the locations shown, so that the photochemically-promoted oxa-di-π-methane rearrangement can take place.

Scheme 1.7. *The intramolecular Diels-Alder approach to the natural enantiomeric form of the isocyanoallopupukeanane framework*



A challenge with the assembly of compound **63** through a Diels-Alder reaction arises from the fact that the side-chain needs to be in an *exo*-position with respect to the double bond and in a "pseudo-*meta*" relationship with the methyl group. This is "in conflict" with the normal outcome of a Diels-Alder reaction, which usually favours an *endo*-product and a "pseudo-*ortho*" relationship of the substituents arising from the diene and dienophile.

It was envisaged that compound **63** could be obtained from the enantiomerically pure *cis*-1,2-dihydrocatechol **59**, which provides the diene component required for the pivotal Diels-Alder reaction. This substrate is readily available in gram quantities through the enzymatic dihydroxylation of toluene by mutant strains of certain bacteria.[27] For the purpose of implementing the proposed synthetic plan, the hydroxy group that is more remote from the methyl group would need to be protected. In addition, the dienophile **66** had to be prepared. The diol moiety on the latter, which will become the side-chain required for the planned intramolecular alkylation reaction later in the sequence, has to be protected since the unprotected form would be prone to participate in a deleterious lactonisation process as explained in detail in Chapter 2. The dienophile moiety would be attached to the diene through an esterification reaction and then subjected to an intramolecular Diels-Alder reaction. Only one adduct is expected to form, as the linker chain of the Diels-Alder substrate **65** is short and thus constrains the dienophile to approach the diene in a way that only leads to an *exo*-type addition product. Under these conditions, the side-chain on the dienophile is guided into a "pseudo-meta" position relative to the methyl group. Furthermore, due to the *Z*-configuration of the dienophile double bond, the pendant chain would be in an *exo*-position relative to the double bond in the product molecule. This, in turn, would create the desired stereocentre on the bridge of the bicyclic adduct.

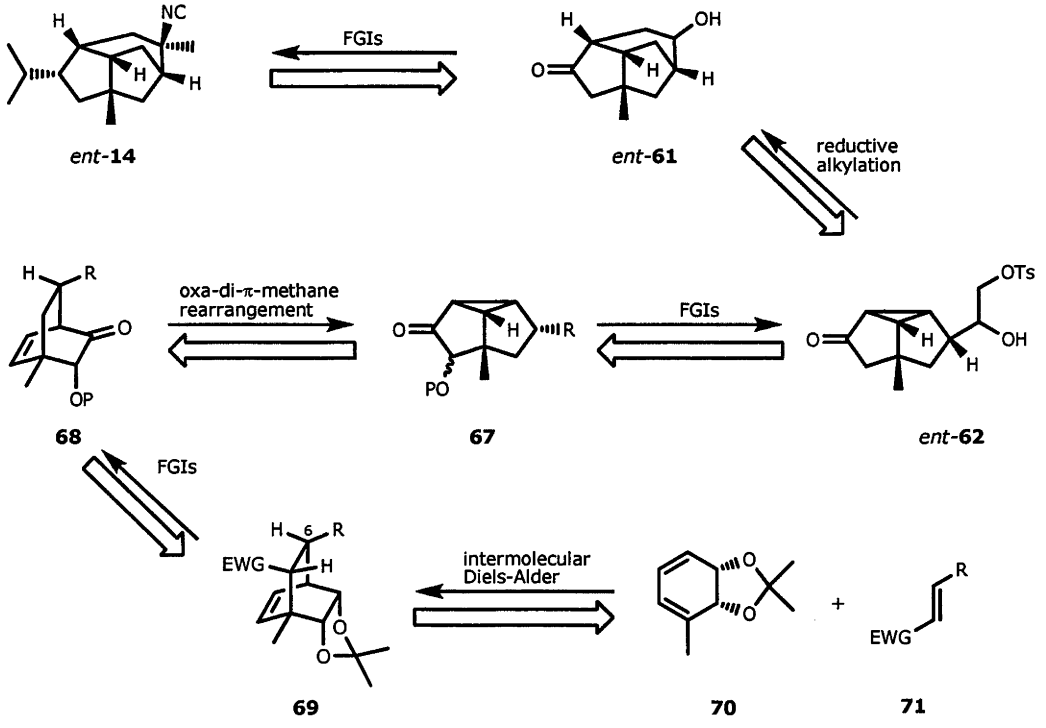
1.6.2 A strategy towards the non-natural enantiomer of the target compound

In addition to the route described in the preceding Section, a modified one was considered. This approach employs the same three key-steps as the one presented immediately above (Section 1.6.1). However, instead of involving an intramolecular Diels-Alder reaction, an intermolecular variant would be chosen as the first key step. It has been shown previously that a protected form of diene **59**, *viz.* acetonide **70**, readily engages in high-pressure promoted Diels-Alder reactions.[26,28] The product of such a reaction with dienophile **71** was expected to be adduct **69** (Scheme 1.8). After the electron-withdrawing groups are removed, it becomes

obvious that the latter has a pseudo-enantiomeric relationship with intramolecularly-derived Diels-Alder adduct **64**. This means that the outcome of the new route would be the production of the non-natural enantiomeric form of 2-isocyanoallopupukeanane. A similarly enantio-divergent pair of reaction sequences has previously been applied by the Banwell group in syntheses of the triquinane-type natural products hirsutene, hirsutic acid and complicatic acid.[26,28] In these cases it was established that by controlling the facial selectivity of the Diels-Alder cycloaddition reaction (achievable by using either the protected or unprotected toluenediol starting material) then either enantiomeric form of the adduct was available.

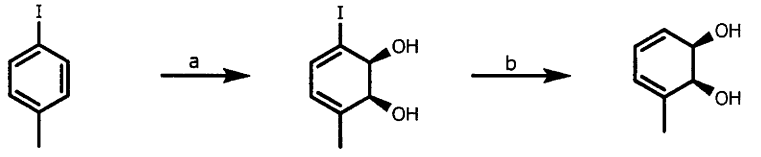
The intermolecular Diels-Alder reaction in this proposed alternative sequence was expected to give a product wherein the electron withdrawing group that promotes the reaction is in an *endo*-orientation relative to the double bond. Since an *endo*-Diels-Alder adduct is expected to form, the double bond of the dienophile **71** will have to have an *E*-configuration so that the pendant chain can adopt an *exo*-orientation relative to the double bond within product **69**. This would create the desired stereocentre at C6. After the Diels-Alder step, the electron withdrawing group would have served its purpose and could thus be removed.

Scheme 1.8. *The intermolecular Diels-Alder approach to the non-natural enantiomeric form of the isocyanoallopupukeanane framework*



The remainder of the synthesis would then follow the pathway that has already been described in Section 1.6.1, except that the non-natural enantiomeric form of the target ultimately would be generated. It was expected that the route mentioned in this Section could later be applied to the preparation of the natural enantiomer of 2-isocyanoallopupukeanane, by using the enantiomer of toluenediol **59** as starting material. The latter can be prepared in a two-step procedure starting from 4-iodotoluene (**72**) (Scheme 1.9).[29,30]

Scheme 1.9. *The preparation of* ent-***59***



4-iodotoluene (**72**) **73** *ent*-**59**

Reagents and conditions: (a) *Pseudomonas putida* UV4 or *Escherichia coli* JM109 (pDTG601); (b) H_2, Pd/C, MeOH, 18°C.

1.7 Conclusion

Two synthetic strategies have been proposed in this Chapter, one leading to 2-isocyanoallopupukeanane, the other to its non-natural enantiomer. The next three Chapters detail efforts to implement such strategies. Each Chapter deals with the work directed toward the execution of one of the three key-steps. Thus, Chapter 2 presents the synthesis of a diverse range of Diels-Alder substrates and adducts. Chapter 3 describes how some of these adducts were transformed into photochemistry precursors and the type of products that were obtained in the oxa-di-π-methane rearrangement. Finally, Chapter 4 presents the work associated with the last part of the synthesis in which the assembly of the tricyclic framework of 2-isocyanoallopupukeanane was completed.

1.8 References

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Chapter 2

First key-step: Diels-Alder reactions

2.1 Introduction

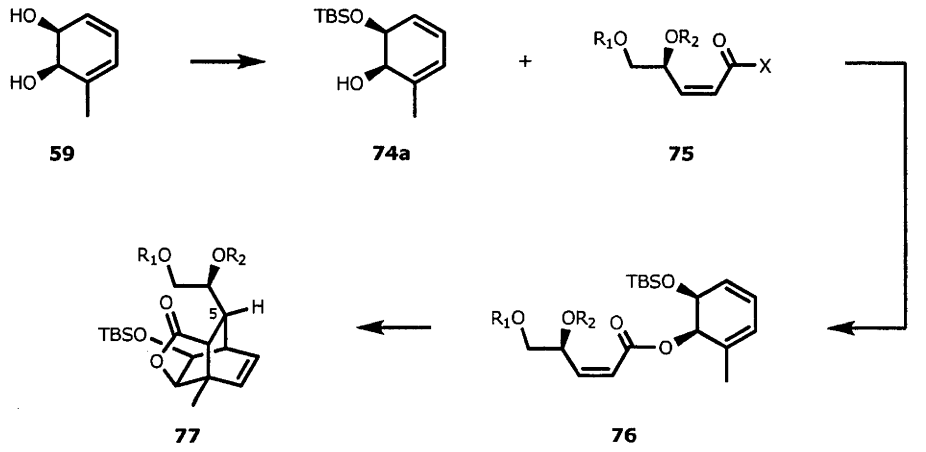
In the previous Chapter retrosynthetic analyses of the target natural product 2-iso-cyanoallopupukeanane and its enantiomer were described. These analyses identified a Diels-Alder reaction as the initial key step. Diels-Alder reactions are [4+2] cycloaddition processes wherein an s-*cis*-diene reacts with a dienophile to form a cyclohexene ring. In a normal electron-demand process, the HOMO of the diene and LUMO of the dienophile interact.[1] The closer these two frontier orbitals are in energy, the more readily the reaction will occur. Electron-donating groups on the diene will increase the energy of its HOMO, while electron-withdrawing groups (EWGs) will lower the LUMO of the dienophile.

In this chapter, different strategies for preparing suitable partners for the Diels-Alder reaction and the outcome of attempts to effect this key pericyclic reaction are discussed. Overall, the reactions that were carried out can be divided into two distinct subclasses, namely intramolecular and intermolecular ones. Both reactions yield bicyclo[2.2.2]octenes through the addition of a dienophile that carries an electron-withdrawing group, such as a carbonyl or a cyano functionality, to a diene moiety that is derived from the toluenediol **59** introduced in Chapter 1. The mildly electron-donating methyl group on the latter facilitates the participation of the diene in the cycloaddition reaction.

Substrates of the basic form **76** (Scheme 2.1) were used to investigate the intramolecular cycloaddition reactions. A central element within this species is the

double bond on the side chain, which is required to be in a *Z*-configuration in order to establish the correct stereochemistry at C5 in Diels-Alder product **77**. Another important structural feature of substrate **76** is the short length of the tether that links the diene and dienophilic components. As a consequence, the cycloaddition step inevitably leads to *exo*-product **77**. Such an outcome stands in contrast to the usual preference for the formation of *endo*-products in Diels-Alder reactions (Alder's rule). Adduct **77** has stereocentres in place that would lead to the natural enantiomeric form of the target natural product if the reaction sequence shown in Chapter 1 is followed.

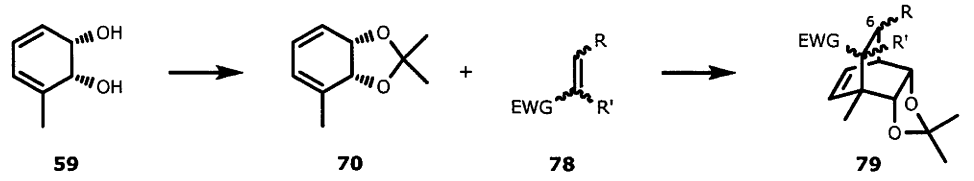
Scheme 2.1. *General scheme for the intramolecular Diels-Alder reactions*



R_1 = R_2 = -$C(CH_3)_2$-, Bn, -(CO)-; X = OH, Cl, OMs, OCO^tBu,

The intermolecular variant of the Diels-Alder reaction mentioned above is expected to yield key adduct **79** (Scheme 2.2). Thus, as the diene **70** and dienophile **78** approach each other, a favourable interaction between the relevant orbitals of the EWG on the dienophile and the developing double bond on the diene should favour an *endo*-type transition state and thus lead to an *endo*-product as the major adduct wherein the directing substituents of the two original substrates are in a pseudo-*ortho* relationship to one another (as predicted by the *ortho*-rule). In order to establish the desired stereocentre at C6 (when R ≠ H), with the R group residing "above" the oxygen functionalities, the R and EWG groups on reactant **78** must have a *trans*-relationship with respect to one another. The thus established stereocentres on adduct **79** would ultimately lead to the production of the non-natural enantiomeric form of 2-isocyanoallopupukeanane, as has already been described in Chapter 1 (see Scheme 1.8, Page 15).

Scheme 2.2. *General scheme for the intermolecular Diels-Alder reactions*



59 **70** **78** **79**

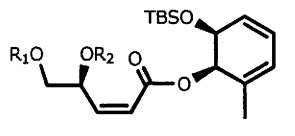
R = C[$CH_2OC(CH_3)_2O$], H; R' = Cl, H; EWG = CHO, CN

There are many ways of promoting Diels-Alder reactions. Traditionally the reactions have been conducted under thermal conditions.[2] Later it was found that Lewis acid catalysts can promote Diels-Alder reactions and thereby reduce or eliminate the need to employ elevated temperatures.[3] Another method involves conducting the reactions at high-pressure (1-19 kbar). While Lewis acid-catalysed reaction conditions cannot be employed in the present context because of the tendency of toluenediol-derived substrates to undergo elimination and concomitant aromatisation, both thermal[4-6] and high-pressure[7,8] reactions have been successfully employed with these types of substrates.

The following Section (2.2) describes the efforts directed towards implementing an intramolecular Diels-Alder reaction of the type described above, while Section 2.3 deals with the corresponding intermolecular cycloaddition process and the results that were obtained therefrom.

2.2 Intramolecular Diels-Alder (IMDA) reactions

Work directed towards the synthesis of a compound of the general structure **76** (Figure 2.1) is described in this Section. A common strategy involves linking of a carboxylic acid derivative **75** to the more hindered hydroxyl group on diene **74a** (Scheme 2.1). A considerable amount of effort was directed towards formation of the desired ester linkage, which is used both to activate the dienophile for the IMDA reaction and as a "disposable" tether[9] to constrain the stereochemical outcome of the reaction. The ester linker brings the diene and the dienophile together temporarily in order that they can take part in a type I IMDA reaction. Upon completion of the cycloaddition reaction the linking group would then be removed.



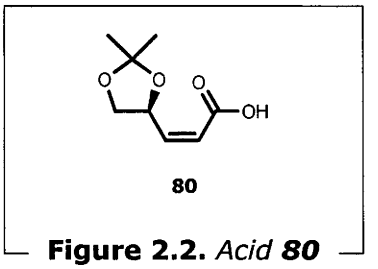
76

R_1 = -$C(CH_3)_2$-, OBn, -(CO)-
R_2 = -$C(CH_3)_2$-, OBn, -(CO)-

Figure 2.1. *Ester **76***

The intramolecular Diels-Alder reactions presented in this Section have been carried out under thermal conditions (80-120°C) – these conditions were effective enough to make a consideration of the use of other methods (especially those involving the use of high pressure) irrelevant.

2.2.1 Early attempts at esterification



80

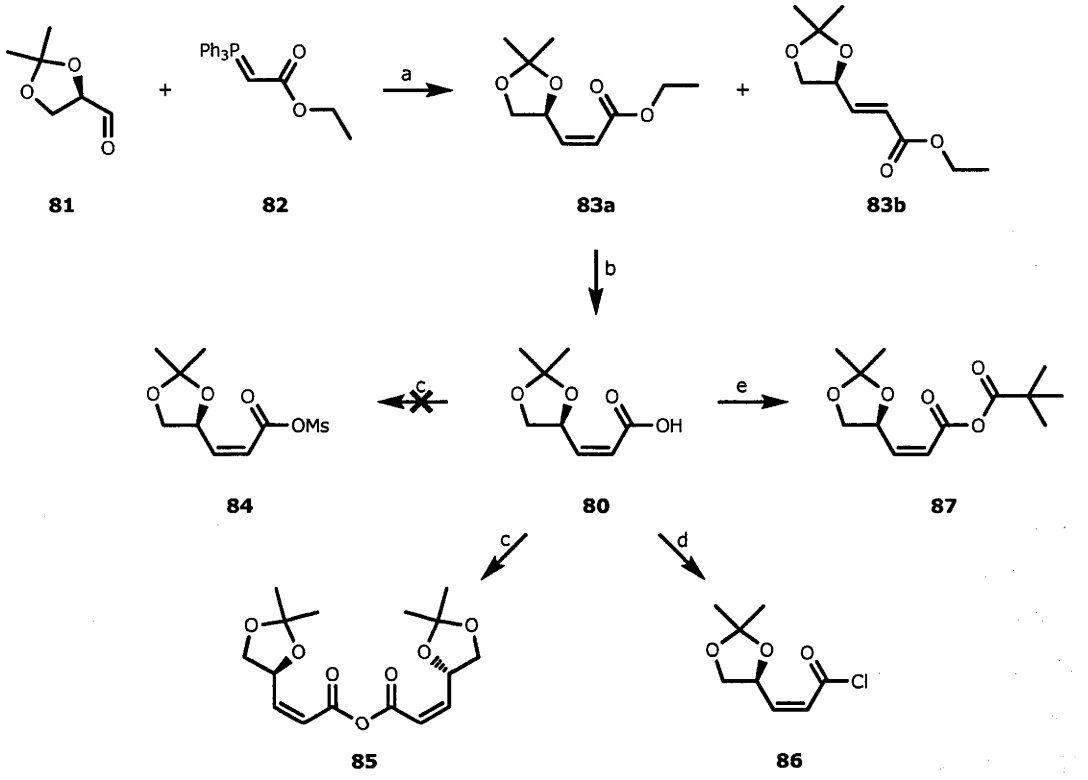
Figure 2.2. *Acid **80***

Work began with the assembly of a Diels-Alder precursor of the general form **76** (Figure 2.1). The synthesis of the dienophilic portion of this molecule was the first task to be undertaken, and to such ends the known[10] *Z*-alkenoic acid **80** (Figure 2.2) was prepared in two steps starting from glyceraldehyde acetonide **81**[11,12] (Scheme 2.3). Treatment of the latter with ethyl (triphenylphosphoranylidene)acetate **82** at room temperature for 23 h gave a mixture of ethyl esters **83a** and **83b**.[12-14] When this Wittig reaction was carried out in methanol, the *Z*-ester was favoured over its *E*-isomer to the extent of 3.5:1. The two isomers were chromatographically separable and identified through the magnitude of the vicinal ^{1}H-^{1}H coupling of the relevant olefinic protons as observed in their respective ^{1}H NMR spectra. Thus, this coupling constant was 11.7 Hz for isomer **83a**, in accord with that of a *cis*-disubstituted alkene, while the *trans*-ester **83b** displayed a significantly larger coupling (J = 15.6 Hz). Compound **83a** was hydrolysed with aqueous NaOH to give, after acidic work-up, compound **80**.

With carboxylic acid **80** in hand, the next step was to activate the acid towards esterification. However, attempts to convert the acid into mixed anhydride **84** by reaction with methanesulfonyl chloride failed (Scheme 2.3). Amongst a large amount of unidentified and polar material the only product that could be characterised, and then only tentatively, was the symmetric anhydride **85**. A similar outcome has been reported previously during the preparation of acyl mesylates of several α,β-unsaturated and other carboxylic acids.[15] Sadly, the yield of the derived product was a meagre 4-6%. As a result efforts in this area were abandoned. Instead, attention was turned towards the preparation of acyl chloride **86**. To avoid cleavage of the sensitive acetonide ring, acid-free conditions were employed. Under one such set of conditions, the carboxylic acid was first deprotonated with base and the resulting anion then treated with oxalyl chloride. Regrettably, this approach did not yield the desired acid chloride. A protocol using a mixture of triphenylphosphine and carbon tetrachloride[16] was also tested.

Unfortunately, these conditions caused the isomerisation of the double bond and formation of the *E*-isomer of the starting material. So, and after numerous such attempts, the preparation of an acyl chloride was deemed unpractical.

Scheme 2.3. *Preparation of derivatives of acid* ***80***



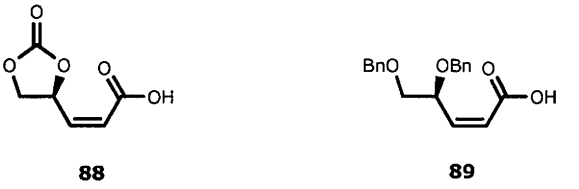
81 **82** **83a** **83b** **84** **80** **87** **85** **86**

Reagents and conditions: (a) MeOH, -10°C→18°C, 23h; (b) NaOH aq, 18°C, 15 h; (c) MsCl, DIPEA or Et_3N, CH_2Cl_2, 0°C, 0.5 h; (d) see text; (e) pivaloyl chloride, 4-methylmorpholine, THF, -5°C, 0.7 h.

In a final effort to obtain the desired acylating agent, unsymmetrical anhydride **87** was prepared using published procedures.[17] The crude product was filtered through neutral alumina and immediately treated with toluenediol **59** under basic conditions. Disappointingly, none of the hoped-for ester was observed and ^1H NMR analysis of the crude mixture revealed that complete aromatisation of substrate **59** had taken place.

In an effort to improve on the outcomes described above, a means of synthesising a carboxylic acid similar to species **80** but incorporating a diol protecting group that is less sensitive towards acids was sought. To such ends, the preparation of acids **88** and **89** (Figure 2.3) was pursued. One approach that seemed straightforward for this purpose was cleavage of the acetonide-protecting group on ester **83a** and subsequent reprotection of the resulting diol as a cyclic carbonate or with individual *O*-benzyl groups. Such attempts have been reported in the literature, with the

outcome being an undesirable cyclisation reaction between one of the liberated hydroxyl groups and the carbonyl centre to form a stable α,β-unsaturated γ-lactone.[12] Therefore, the route *via* glyceraldehydes that already carry the relevant protecting group was followed.

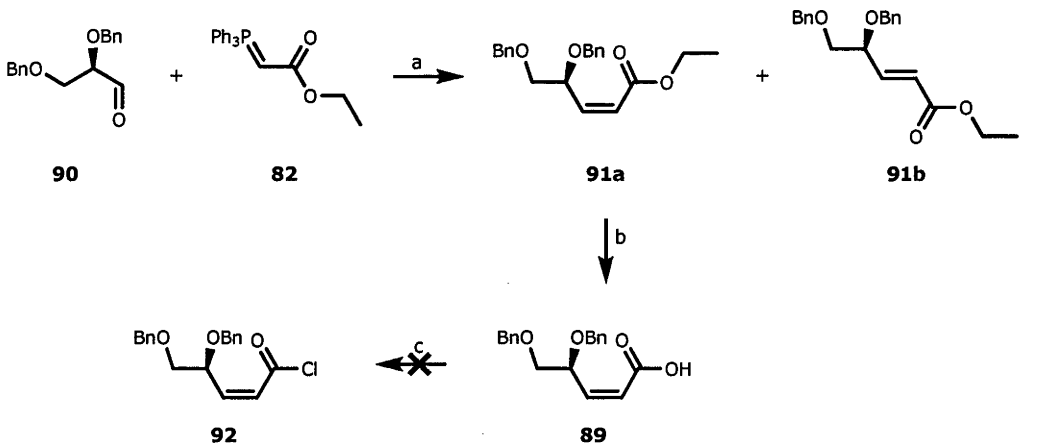


88 **89**

Figure 2.3. *Carboxylic acids **88** and **89***

The preparation of compound **88** was explored briefly but difficulties arising from the solubility of compounds incorporating the carbonate protecting group made synthetic work particularly difficult. In contrast, compound **89** proved easy to prepare. The synthesis started from the known[18] aldehyde **90** which was subjected to a Wittig reaction with ethyl (triphenylphosphoranylidene)acetate **82** to give a 2:1 mixture of *Z*- and *E*-esters **91a** and **91b** (Scheme 2.4). After chromatographic separation of the two isomers, ester **91a** was subjected to base-promoted hydrolysis. However, treatment of the resulting acid **89** with oxalyl chloride did not lead to the target acid chloride **92**. Rather, partial or complete cleavage of the *O*-benzyl ether units, followed by the aforementioned and undesired lactonisation process, was observed.

Scheme 2.4. *Attempted preparation of acid chloride **92***

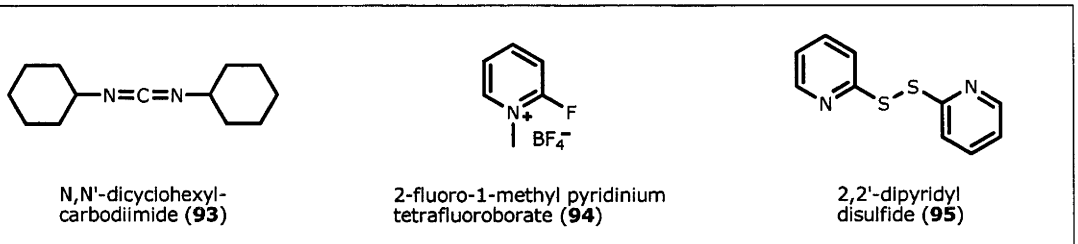


90 **82** **91a** **91b**

92 **89**

Reagents and conditions: (a) MeOH, 0°C→18°C, 17 h; (b) NaOH aq, MeOH, 22°C, 23 h (c) $(COCl)_2$, DMF, CH_2Cl_2, 0°C→18°C, 18 h.

Given the failure to activate the carboxylic acid functionality with methanesulfonyl or pivaloyl chloride, or through conversion into an acyl chloride following standard methods, attention was turned to other esterification methods, a few of which are mentioned here. Esterification of carboxylic acids has been carried out successfully in presence of diverse reagents such as N,N'-dicyclohexylcarbodiimide (DCC, **93**), 2-fluoro-1-methyl pyridinium tetrafluoroborate (**94**) and 2,2'-dipyridyl disulfide (**95**) (Figure 2.4).



N,N'-dicyclohexyl-carbodiimide (**93**)

2-fluoro-1-methyl pyridinium tetrafluoroborate (**94**)

2,2'-dipyridyl disulfide (**95**)

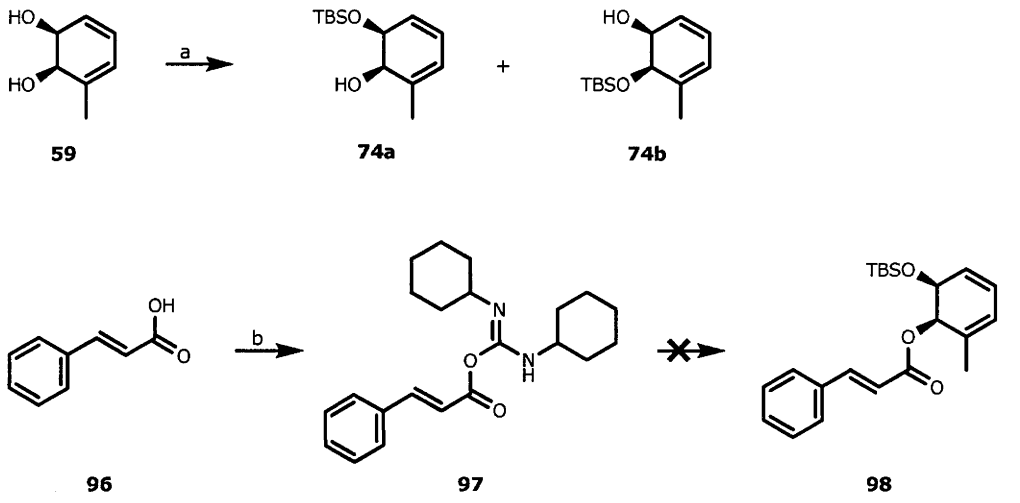
Figure 2.4. *Examples of activating or coupling agents used for esterification*

The first-mentioned reagent is a dehydrating agent that activates the carboxylic acid starting material *in situ* – DCC adds onto the acid group to create a reactive species that is substituted by an alcohol. A preliminary study of this type of reaction using commercially available *E*-cinnamic acid as a model compound was carried out as detailed below.

The sequence started with the mono-protection of toluenediol **59** that gave a mixture of the mono-protected diols **74a** and **74b** (Scheme 2.5), in ratios as varied as 5:1 and 2:1. The formation of product **74a** is favoured due to an introduction of the bulky TBS group at the sterically less hindered hydroxy group (*viz.* at that one remote from the methyl group). After chromatographic separation of the mixture, isomer **74a** was treated with cinnamic acid (**96**) in the presence of DCC following a procedure involving similar types of substrates.[19] However, the desired ester, **98**, was not observed. Instead, it appeared that the reaction mixture consisted of a 1.8:1.2:1 mixture of acid **96**, mono-protected diol **74a** and the DCC-adduct **97**. The ^{1}H NMR spectrum of a purified sample of compound **97** showed a broad signal at δ 7.1 and the IR spectrum revealed an absorption band at around 3300 cm^{-1}. These spectral features suggest the presence of an N-H proton within the product. Similar values have been detected in the relevant spectra of other compounds that carry a $CO_2C(NHR)=NR$ moiety.[20] Other peaks in the ^{1}H NMR spectrum of carbamimidic anhydride **97** largely follow the pattern of a spectrum that has been published previously.[21] When the above-mentioned coupling reaction was repeated with acid **80** only starting material could be recovered. The addition of reagents

such as HOBt, triethylamine and pyridine to the reaction mixture, or replacing DCC with EDC, did not improve the outcome.

Scheme 2.5. *Attempts at esterification with DCC*

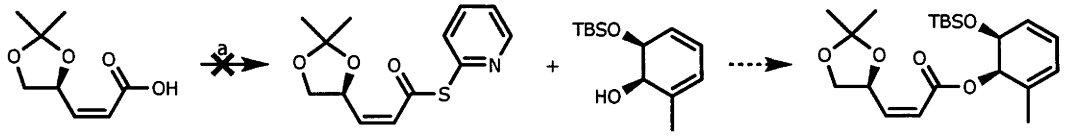


Reagents and conditions: (a) imidazole, TBS-Cl, CH_2Cl_2, 18°C, 2 h; (b) **74a**, DCC, CH_2Cl_2, 0°C, 0.3 h.

A number of immonium-, pyridinium- and thiazolium-type reagents have proved useful for peptide coupling.[22] On this basis one such reagent, 2-fluoro-1-methyl pyridinium tetrafluoroborate (**94**) (Figure 2.4), was synthesised and employed in the esterification of diol derivative **74a** with carboxylic acid **80**. Once again, however, only the starting materials were recovered from the reaction.

The Corey-Nicolaou procedure for macrolactonisation[23] was adapted in an effort to effect esterification of acid **80** with diol derivative **74a** (Scheme 2.6). This method involves initial conversion of the carboxylic acid into the 2-pyridinethiol ester by treatment of the former with 2,2'-dipyridyl disulfide (**95**) (Figure 2.4) and PPh_3. Coupling of an alcohol with the resulting thiol ester is normally accomplished by heating a mixture of the two compounds. This esterification procedure was expected to be suitable as it is conducted under neutral conditions, thereby enhancing the chances of survival of the fragile acetonide group associated with substrate **80**. When this compound was treated with 2,2'-dipyridyl disulfide and PPh_3, signals corresponding to the acetonide methyls could still be seen in the ^1H NMR spectrum of the crude product, however, the olefinic signals had disappeared. Such data suggested that, instead of the expected formation of thiol ester **99** taking place, Michael addition of a pyridinethiol moiety to the double bond had occurred.

Scheme 2.6. *Esterification via thiol ester* ***99***



80 **99** **74a** **100a**

Reagents and conditions: (a) **95**, PPh_3, toluene, 18°C, 20 h.

A search of the literature revealed an instance where EDCI and BOP-based reagents had failed to cause esterification, while Yamaguchi conditions[24] had delivered the desired coupling product.[25] This seemed like a very promising method and lead to the study described in the next Section.

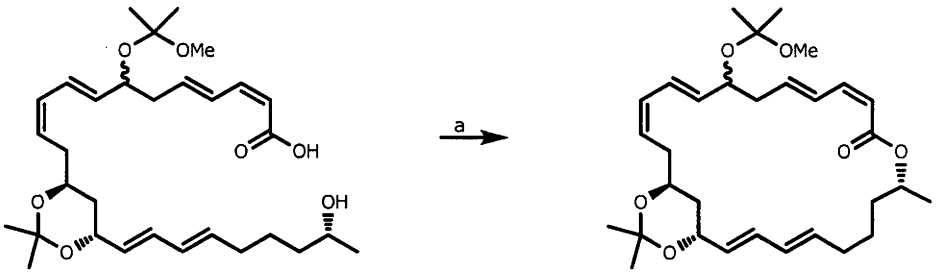
2.2.2 Examination of Yamaguchi esterification and related reactions

The Yonemitsu modification[26] of the Yamaguchi esterification reaction was investigated as a means of preparing the desired ester **100a** from precursors **74a** and **80**. Thus, carboxylic acid **80** was treated with 2,4,6-trichlorobenzoyl chloride and Et_3N, then a mixture of DMAP and mono-protected diol **74a**. As a result a single compound was obtained but this appeared to be an *E*-configured ester, which was deduced by examination of the resonances arising from the olefinic protons observed in the ^1H NMR spectrum. Whereas the relevant signals in acid **80** showed a coupling constant of 11.7 Hz, those in the esterification product were of the order of 15.5 Hz. A more thorough search of the literature revealed that other research groups had observed similar isomerisation processes during both esterification[27] and lactonisation[28,29] reactions. The isomerisation is attributed to the conjugated *Z*-double bond taking part in a reversible Michael type reaction with triethylamine and/or DMAP that leads to the preferential formation of the thermodynamically more stable *E*-isomer. [30,31]

In contrast to the above-mentioned results, one research group has reported the successful Yamaguchi macrolactonisation of polyunsaturated tetracosanoic acid derivative **101** (Scheme 2.7) as part of a three-step procedure in which an ester precursor of acid **101** was converted into the natural product (-)-macrolactin A and an epimer.[32] Thus, a THF solution of the triethylamine salt of acid **101** was treated with the Yamaguchi reagent (2,4,6-trichlorobenzoyl chloride). After evaporation of

the solvent, the residue was dissolved in toluene and added to DMAP. The outcome of the reaction was the formation of macrolactone **102**. It appears that isomerisation of the *Z*-configured double bond within the (*E*,*Z*)-dienoic acid moiety did not take place during this process.

Scheme 2.7. *Yamaguchi macrolactonisation of hydroxyacid* ***101***



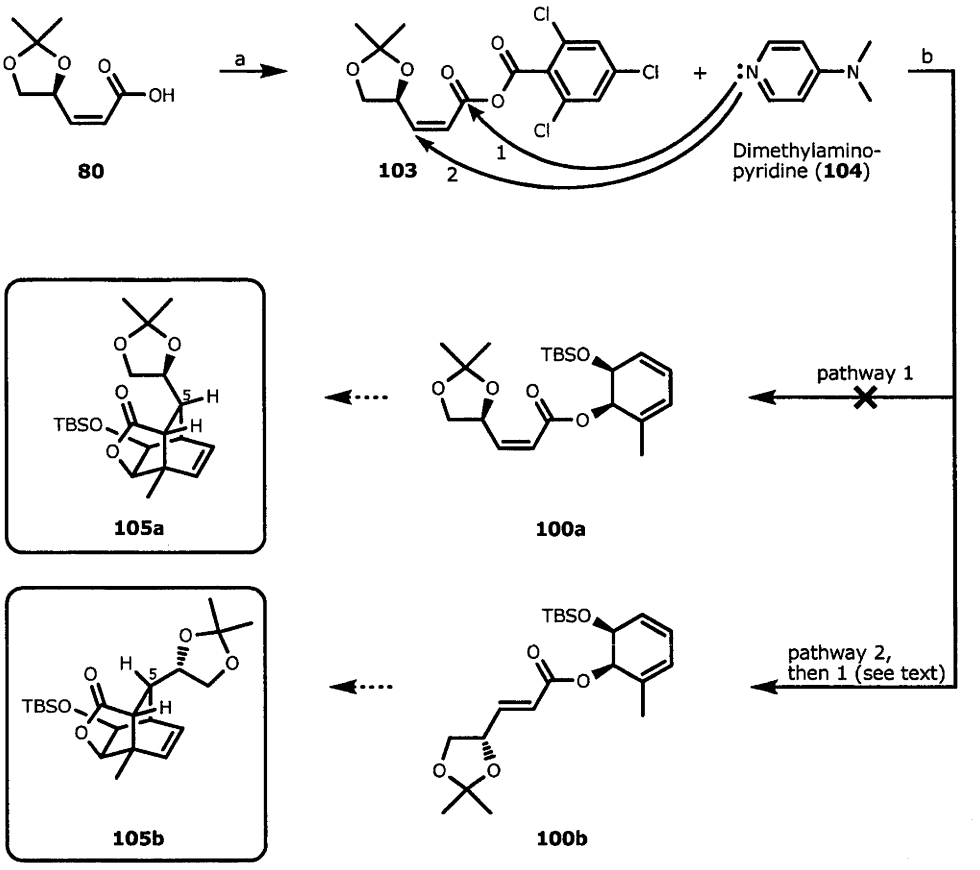
101 **102**

Reagents and conditions: (a) (i) Et_3N, diethyl ether; (ii) 2,4,6-trichlorobenzoyl chloride, THF, 18°C, 12 h; (iii) DMAP, toluene, 18°C, 1.5 h.

A proposed path for the isomerisation reaction observed in the present case is detailed in Scheme 2.8. Thus, it is thought that the carboxylic acid first reacts with the Yamaguchi reagent in a normal fashion to form mixed anhydride **103**. DMAP normally acts as acyl transfer agent and was thus expected to attack anhydride **103** at the carbonyl site adjacent to the double bond as shown in pathway 1 of Scheme 2.8. The intermediate so formed should then engage in an esterification reaction with the alcohol to give ester **100a**. The fact that only *E*-ester **100b** was isolated from the reaction mixture suggests that, in the present case, the reaction initially proceeds *via* pathway 2. In other words, DMAP (or Et_3N) attacks the double bond of the mixed anhydride *via* a Michael addition reaction. The intermediate thus formed can rotate at the temporarily formed single bond. After a retro-Michael reaction the *E*-isomer of anhydride **103** is free to react with DMAP along pathway 1 and then with alcohol **74a**. The end result is production of ester **100b**, which, after a Diels-Alder step, would yield the observed bicyclo[2.2.2]octene **105b**. Regrettably, of course, the stereocentre at C5 in the latter compound is now opposite to that required.*

* Diels-Alder adduct **105b** could be obtained in good yield by heating ester **100b** in toluene. Despite the wrong configuration at C5, lactone **105b** was used as substrate for a brief evaluation as to what extent this type of compound could be further elaborated along the planned synthetic route. Details to this study are presented in the next Chapter (Section 3.2).

Scheme 2.8. *Yamaguchi esterification of acid **80** with toluenediol **74a***



Reagents and conditions: (a) 2,4,6-trichlorobenzoyl chloride, Et_3N, toluene, 18°C, 2 h; (b) **74a**, 18°C, 20 h.

While efforts to identify reaction conditions that suppress the $Z \rightarrow E$ isomerisation reaction were made, a survey of the relevant literature indicates that even when various elements such as bases and acylating agents are changed it is often very difficult to stop such processes.[29] Nevertheless, the esterification process described above was repeated following a different method in which carboxylic acid **80** is first activated with methanesulfonyl chloride. The resulting mixed anhydride was then treated with DMAP and alcohol **74a**. This type of reaction has been successfully carried out at low temperatures (-25 → -10°C).[33] However, acid **80** and alcohol **74a** failed to react even at -10°C although, significantly, isomerisation of the double bond within the former substrate was observed once again.

In order to try and establish when the isomerisation takes place, acid **80** was dissolved in THF and cooled to approximately -80°C. After a reference ^1H NMR spectrum was recorded, Et_3N and methanesulfonyl chloride were added successively and the mixture stirred at -80°C for 30 minutes. After acquiring another ^1H NMR spectrum, the course of the reaction was followed as it was slowly warmed at

increments of about 10°C, and then kept at each new temperature for ten minutes. After each warming period, a small sample of the reaction mixture was collected and transferred into an NMR tube that was cooled to the relevant temperature. The sample was quickly diluted with deuterated benzene and a ^{1}H NMR spectrum acquired. Formation of the anhydride of acid **80** was observed right from the start. Even though the conversion appeared slow at -78°C (two sets of signals due to *cis*-related olefinic protons observed), it was complete after an additional ten minutes at -70°C. Inspection of the olefinic proton signals attributed to the anhydride showed a coupling constant expected of a *cis*-double bond over the whole test range of (-80)-20°C. The same *cis*-double bond signal was observed even after the mixture was stirred at ambient temperature overnight. Such experiments tend to suggest that Et_3N does not cause the observed isomerisation. The same mixture was cooled once again to -78°C, and a premixed solution of DMAP and alcohol **74a** in THF was now added slowly. After stirring the resulting mixture at -78°C for ten minutes, an aliquot was collected in the same fashion as described above. The ^{1}H NMR spectrum of this aliquot showed signals with the telltale coupling constants of a *trans*-double bond, thus suggesting the acylating agent DMAP facilitates isomerisation, which is complete within ten minutes at -78°C. Since the desired esterification reaction is presumed to take place at much higher temperatures, it becomes obvious that the desired *cis*-ester **100a** would almost certainly not be able to be obtained in the presence of DMAP. In a final attempt to alter the outcome of these types of esterification reactions, the above-mentioned reaction was repeated without DMAP. After stirring the reaction at room temperature overnight, only the starting materials could be recovered. Accordingly, this approach to the target ester was abandoned.

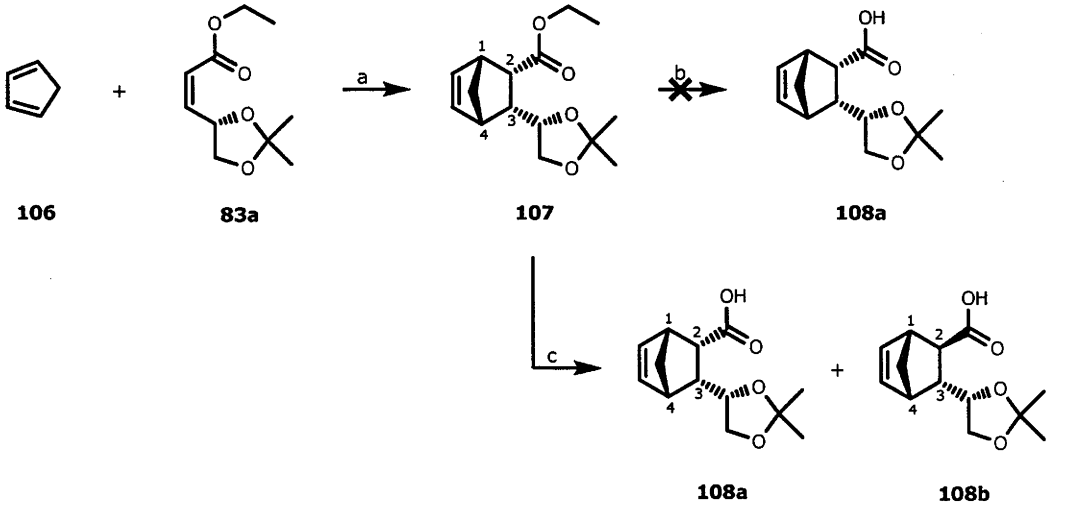
In summary, then, it seemed that no suitable method could be found for the coupling of various *Z*-configured α,β-unsaturated acids and diol derivative **74a**, so other approaches to the target substrate for the IMDA reaction were pursued. Isomerisation problems encountered under Yamaguchi conditions have been previously avoided through masking of the double bond, for example in the form of an alkynoic acid.[29,34] After the esterification of the latter with an alcohol was completed, the *Z*-double bond was introduced through Lindlar-type reduction of the triple bond and thus providing a potentially attractive way around the problem encountered as described above. However, generation of the double bond through Lindlar reduction on the sensitive toluenediol derivative could cause some difficulties in the present case. Accordingly, it was decided to mask the double bond through a Diels-Alder cycloaddition reaction with cyclopentadiene. After esterification involving the masked acid, it was expected that cyclopentadiene could be removed through a retro-Diels-Alder reaction. The outcomes of such masking reactions are described in the next Section.

2.2.3 Masking of the *cis*-alkene prior to esterification

The initial target of the masking group strategy was the known acid **108a**[35] that was prepared as is shown in Scheme 2.9. Thus, following previously reported protocols[36] for making the corresponding methyl ester, compound **83a** was treated with freshly 'cracked' cyclopentadiene (**106**) at -23°C in presence of diethylaluminium chloride. The reaction gave a mixture of stereoisomers in 76% yield with the (*syn-endo*)-adduct **107** predominating. The stereochemistry of this major product **107** was confirmed through comparison of the derived ^{1}H and ^{13}C NMR as well as IR spectral data with those reported in the literature.[37]

The next step in the proposed sequence was to involve the conversion of the ethyl ester into the corresponding carboxylic acid. However, ester **107** turned out to be quite resistant to hydrolysis. The corresponding methyl ester has reportedly been saponified with sodium hydroxide and after acidic work-up acid **108a** thereby obtained in reasonably high yields.[35,37] The saponification of ethyl ester **107** was attempted following the two literature procedures, but each time only starting material was recovered. The use of more concentrated base (2.5 M aqueous solution of sodium hydroxide) did not improve on this result. The hydrolysis mixture was then heated at increasing temperatures. Mild heating (30-60°C) did not have any effect, but stirring the mixture at 80°C overnight lead to complete hydrolysis. Unfortunately these conditions also promoted epimerisation at C2, yielding a 1:2.8 mixture of compounds **108a** and **108b**. The configuration of the former was confirmed through comparison of spectral data with those reported in the literature.[35] The stereo-

Scheme 2.9. *Masking of the double bond with cyclopentadiene (**106**), part I*



Reagents and conditions: (a) Et_2AlCl, toluene, CH_2Cl_2, -23°C, 3 h; (b) 1 M or 2.5 M NaOH aq, with or without THF, 18-60°C, 20 h; (c) 2.5M NaOH aq, MeOH, 80°C, 20 h.

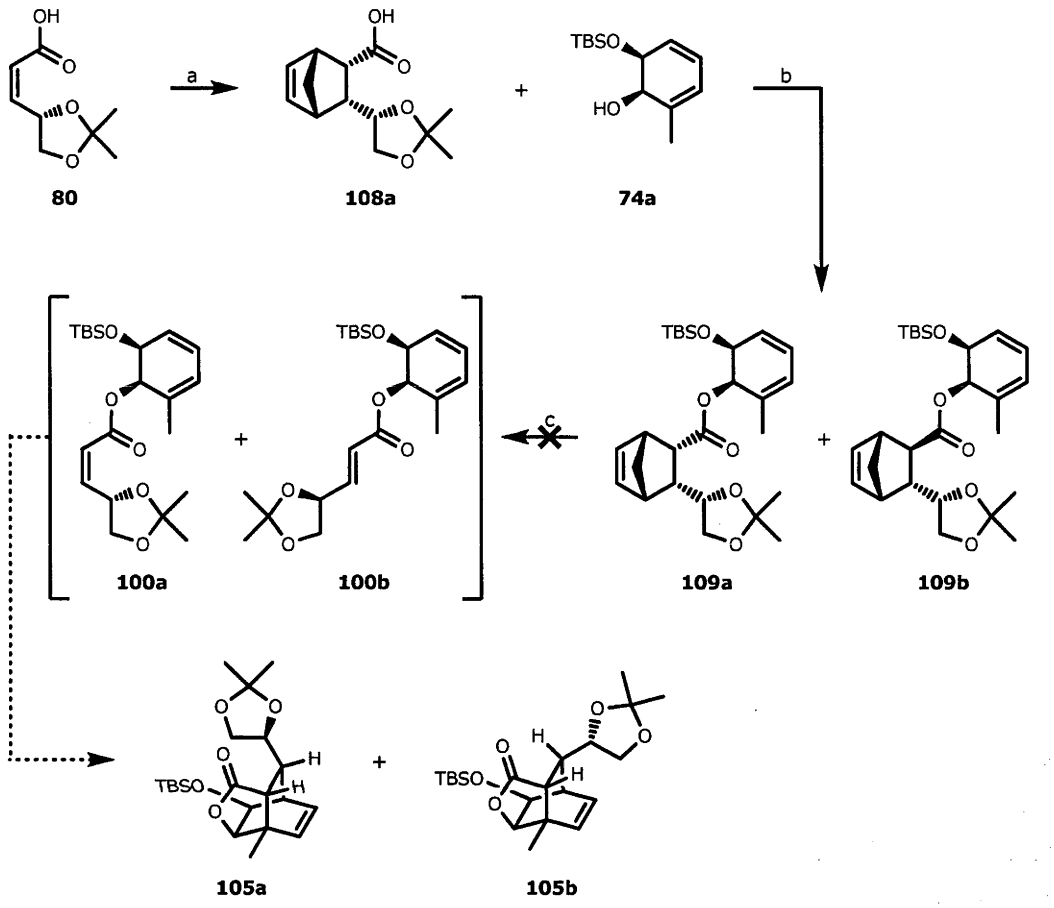
chemistry of epimer **108b** was assigned after the coupling constants of the protons at C1-C4, as recorded at 300 MHz, were compared with those of the relevant methyl ester, the closest match to acid **108b** that is known in the literature.[38] The protons at C2 and C3 in adduct **108b** have a *trans*-relationship and are therefore expected to exhibit a smaller coupling constant than would be observed for the corresponding protons in epimer **108a** ($J_{2,3}$=10.4 Hz, 300 MHz). This is the case and $J_{2,3}$ in the ^{1}H NMR spectrum of compound **108b** is approximately 5.0 Hz, which is exactly the same as obtained with the corresponding methyl ester. On the other hand, in acid **108b** $J_{1,2}$ = 1.5 Hz (1.6 Hz in the methyl ester), whereas $J_{3,4}$ = 3.3 Hz – the same value as observed for adduct **108a** (3.1 Hz) and the corresponding methyl ester (3.4 Hz) described in the literature.

In a different approach, cyclopentadiene was reacted with the free carboxylic acid **80** (Scheme 2.10). After an unsuccessful attempt to catalyse the Diels-Alder reaction using the Lewis acid dimethylaluminium chloride, the diene and dienophile were heated at reflux in benzene without additives. Under these conditions adduct **108a** was obtained as a white solid in 70% yield. The spectral data obtained proved a perfect match for those recorded in the literature.[35] Accordingly, with the desired carboxylic acid **108a** in hand, its esterification with mono-TBS protected toluenediol **74a** was pursued. However, the application of Yamaguchi conditions furnished a 1.2:1 and chromatographically inseparable mixture of epimers **109a** and **109b**. This undesired and inconvenient epimerisation was not thought to be a serious problem as chances were high that the choice of different esterification conditions could prevent epimerisation. However, before looking into improving the ester coupling reaction, an investigation of the validity of a retro-Diels-Alder/Diels-Alder sequence was undertaken (Scheme 2.10, conversion **109a-b** → **105a-b**). To such ends, the epimeric mixture of compounds **109a** and **109b** was heated to 180°C without further ado. The result was complete consumption of the starting materials. However, this led to a complex mixture of compounds. After purification over a silica column only a small amount of what appeared to be a mixture of two compounds could be isolated. While the identity of these products could not be confirmed, the ^{1}H NMR spectrum of this material showed characteristic signals due to the core bicyclo[2.2.1]heptene entity of the substrate mixture. On this basis it was concluded that, whatever else might have happened, the retro-Diels-Alder step had not taken place.

To establish whether the retro-Diels-Alder reaction would work at a lower temperature, epimers **109a** and **109b** were heated at increments of 10°C from 110°C to 150°C. Up until 140°C only starting material was observed. At 150°C a similar mixture to that mentioned above was again observed. It has to be assumed, therefore, that the extremely high reaction temperatures needed for the retro-Diels-

Alder reaction to occur also promote decomposition of the substrate and its delicate diene component.

Scheme 2.10. *Masking of the double bond with cyclopentadiene (**106**), part II*

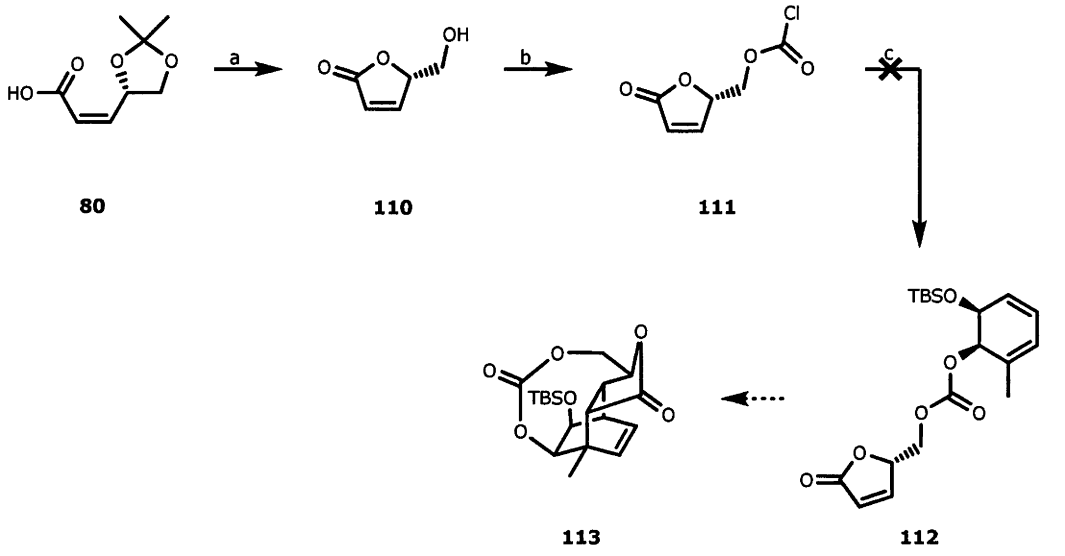


Reagents and conditions: (a) **106**, benzene, 80°C, 17 h; (b) 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, toluene, 18°C, 18 h; (c) 1,2-dichlorobenzene, 180°C, 3 h.

One last effort directed towards the preparation of a substrate for an IMDA reaction was undertaken. As has been mentioned before, compound **80** is prone to acetonide cleavage under acidic conditions and readily forms butenolide **110**[39] as shown in Scheme 2.11. By using the latter to "lock" the double bond into the required *Z*-conformation, the preparation of carbonate **112** was attempted. A successful IMDA reaction was then expected to give an adduct such as **113** that should be convertible into a suitable photochemistry precursor. To these ends, butenolide **110** was treated with triphosgene and pyridine. Formation of the desired chloroformate **111**[40] was not, however, observed. Rather, the reaction mixture consisted, in large part, of a mixture of two compounds. The main component could not be fully identified but appeared to incorporate the butenolide moiety of alcohol **110**. The minor constituent had spectral properties similar to protoanemonin (**114**),[41] which could arise from an elimination reaction on chloroformate **111**, as

suggested in Scheme 2.12, to give an exocyclic double bond. Subjection of the mixture to carbonate-forming conditions with mono-protected diol **74a** did not give the desired product **112**.

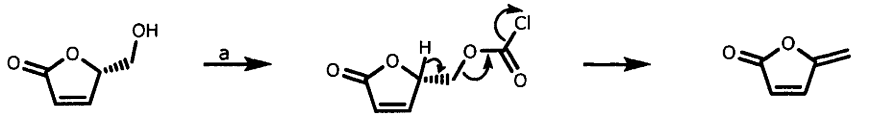
Scheme 2.11. *Masking of the double bond as a butenolide*



80 **110** **111** **113** **112**

Reagents and conditions: (a) H_2SO_4, MeOH, 18°C, 2 h; (b) triphosgene, pyridine, CH_2Cl_2, 0°C→18°C, 3 h; (c) **74a**, *n*-BuLi, THF, -78°C→0°C, 2.5 h.

Scheme 2.12. *A possible mechanism for the formation of protoanemonin (**114**)*



110 **111** protoanemonin (**114**)

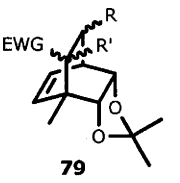
Reagents and conditions: (a) triphosgene, pyridine, CH_2Cl_2, 0°C→18°C, 3 h.

On the basis of the work described to this point, it is clear that the IMDA approach has not been successful, due to difficulties encountered with the esterification reaction required to link diene and dienophile to one another in the required fashion. One reason for the failure of such coupling reactions could be the bulk around the hydroxy group on TBS mono-protected compound **74a**. Another feature that leads to complications is that the α,β-unsaturated carbonyl moiety of the carboxylic acid-based substrates is in the *Z*-configuration. Unfortunately, this arrangement is thermodynamically less stable than its *E*-isomer and thus prone to isomerisation *via* a Michael addition/β-elimination reaction sequence. Avoiding this problem through masking of the double bond was not successful. Given this situation, no further work directed towards the synthesis of a substrate suitable for

an intramolecular Diels-Alder reaction was carried out. Rather, attention was turned towards effecting the intermolecular equivalent of this process. The results of these efforts are described in Section 2.3.

2.3 Intermolecular Diels-Alder reactions

This Section describes the synthesis of intermolecular Diels-Alder adducts of the general form **79** (Figure 2.5). As has been mentioned in Chapter 1, the control of facial selectivity in the Diels-Alder step determines which enantiomeric form of the target compound will be obtained. Thus, the outcome of the route involving a *β*-face selective intermolecular Diels-Alder reaction would be the production of the non-natural enantiomeric form of 2-isocyanoallopupukeanane. It was expected that this same route, if successful, could later be applied to the preparation of the natural enantiomer of 2-isocyanoallopupukeanane by using the known enantiomer of toluenediol **59**, *viz. ent*-**59**, as starting material.



79

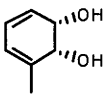
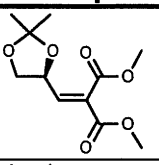
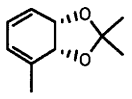
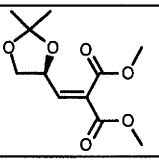
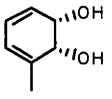
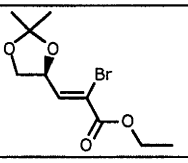
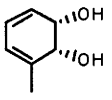
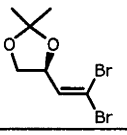
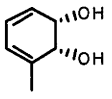
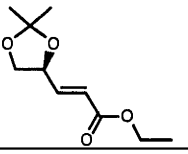
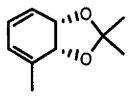
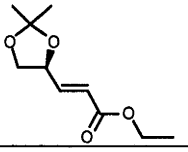
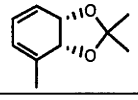
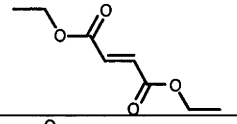
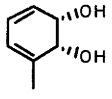
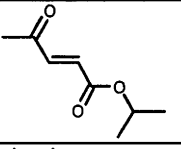
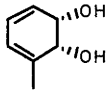
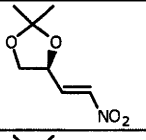
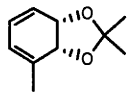
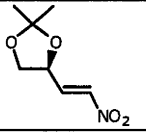
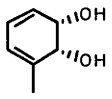
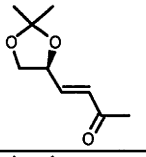
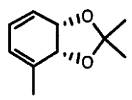
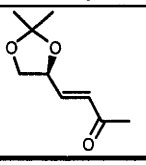
Figure 2.5.

The intermolecular Diels-Alder reactions of toluenediol **59** and its acetonide-protected counterpart **70** with a wide range of dienophiles have been examined previously.[42,43] Building on these results, Diels-Alder reactions with both known and previously untested dienophiles were carried out. The outcomes of such studies are presented in the following Sections.

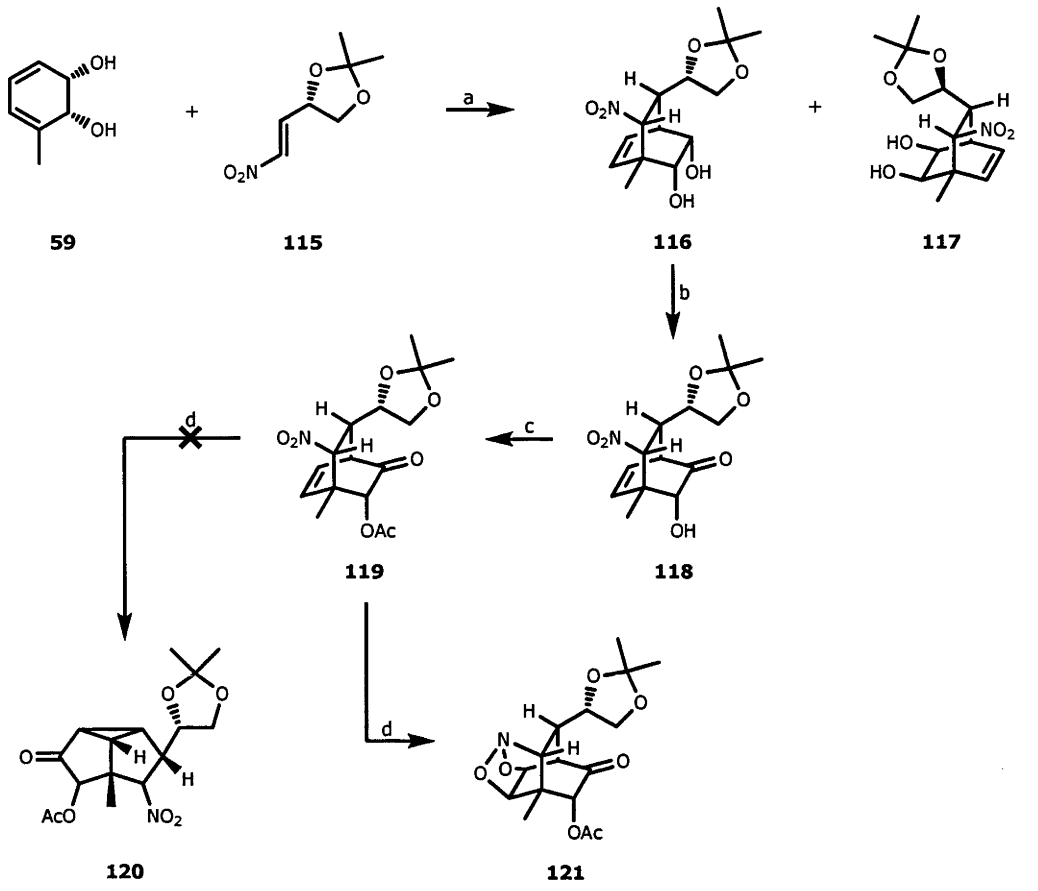
2.3.1 High-pressure Diels-Alder reactions

The outcome of a previous study[42] of intermolecular Diels-Alder processes, carried out under high-pressure conditions (19 kbar, 18°C), is summarised in Table 2.1. So, while several of the Diels-Alder reactions were successful, none of the adducts could be used to complete the synthesis of the target natural product due to complications at some point later in the route. Most notably, one of the product isomers in Entry 9 was taken as far as the photochemistry step (Scheme 2.13).[42] However, photoprecursor **119** did not take part in the expected oxa-di-π-methane rearrangement to give diquinane **120**. Instead, the reaction took an alternative course leading to dioxazolidine **121**. Thus, irradiation of compound **119** caused a [3+2]-cycloaddition reaction between the nitro group and the C-C double bond within the substrate. This type of reaction has been reported on a few occasions, but usually with an aromatic nitro compound,[44-46] and was therefore quite unexpected in this case.

Table 2.1 The results of a previously conducted evaluation of intermolecular Diels-Alder reactions[42]

Entry	Diene	Dienophile	Result
1			Mixture of two isomeric Diels-Alder adducts
2			1:1 mixture of two isomeric Diels-Alder adducts
3			Rearomatised diol → no Diels-Alder reaction
4			Rearomatised diol → no Diels-Alder reaction
5			No reaction
6			No reaction
7			Full conversion, 1:1 mixture of two (inseparable) isomeric Diels-Alder adducts
8			Full conversion, three inseparable isomeric Diels-Alder adducts
9			Differing yields (21-49%), two isomeric Diels-Alder adducts
10			65%, mainly one (desired) Diels-Alder adduct
11			No reaction
12			No reaction

Scheme 2.13. *Formation and chemical manipulation of Diels-Alder adduct* ***116***

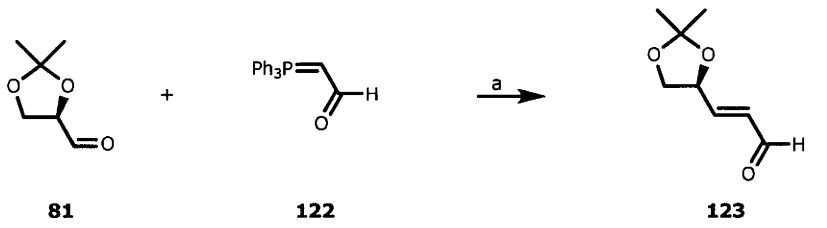


Reagents and conditions: (a) 19 kbar, CH_2Cl_2, 18°C, 24 h; (b) *p*-TsOH·H_2O, 4-AcNH-TEMPO, CH_2Cl_2, 0°C→18°C, 20 h; (c) Ac_2O, pyridine, 18°C, 0.5 h; (d) hν, acetone, 5°C, 16 h.

In an extension of the results listed in Table 2.1, a dienophile with a different electron-withdrawing group was sought. Since an aldehyde moiety is a stronger electron-withdrawing group than an ester it was expected to facilitate the Diels-Alder reaction. Accordingly, dienophile **123** (Scheme 2.14) was chosen for the study discussed immediately below.

Compound **123** was initially prepared by a one-pot procedure that forms aldehyde **81** *in situ* and then reacts this with the appropriate Wittig reagent.[47] The reaction went to completion and aldehyde **123** was obtained in pure form but poor yield (11%). In contrast, when aldehyde **81** was isolated before being treated with the Wittig reagent and using dichloromethane as the solvent, then target dienophile **123** could be obtained in up to 63% yield.

Scheme 2.14. *Preparation of aldehyde **123***

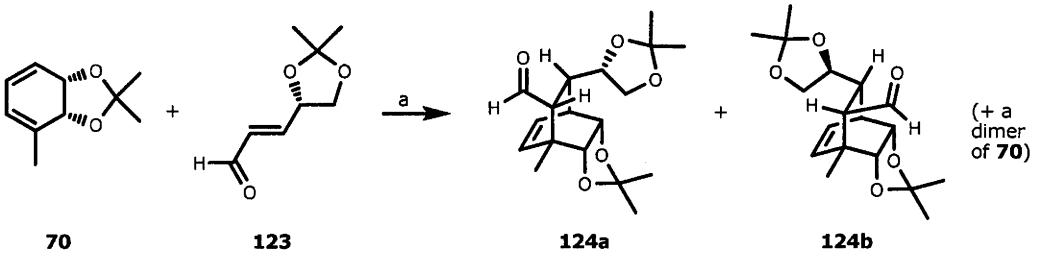


81 **122** **123**

Reagents and conditions: (a) CH_2Cl_2, 18°C, 16 h.

An initial test of the Diels-Alder reaction between diene **70** and aldehyde **123** was carried out at elevated temperatures (benzene at 80°C or toluene at 120°C). The result was the complete recovery of both starting materials. A switch to high-pressure conditions (19 kbar, 18°C) resulted in the full conversion of the substrates into a chromatographically inseparable and *ca.* 1:1 mixture of diastereomers **124a** and **124b**, and a small amount of a previously reported dimer of diene **70**[8] (Scheme 2.15). It was found that the highest product yields were obtained when a 1:1 mixture of substrates **70** and **123** was used in the cycloaddition step. For characterisation purposes the component parts of a small sample of the mixture of products **124a** and **124b** was separated by HPLC, but the two compounds were otherwise carried forward as a mixture. The structures of these adducts were confirmed by a combination of 1- and 2-D NMR spectroscopic methods, as well as IR spectroscopic and mass spectral analyses.

Scheme 2.15. *The intermolecular Diels-Alder reaction between substrates **70** and **123***



70 **123** **124a** **124b**

Reagents and conditions: (a) 19 kbar, CH_2Cl_2, 18°C, 24 h.

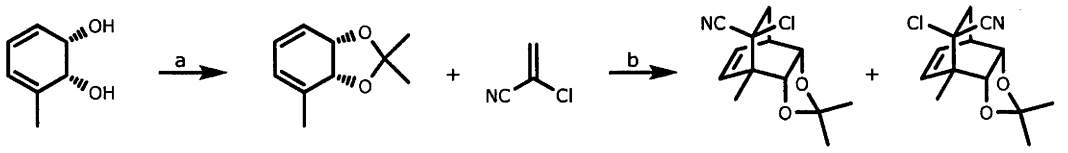
Various efforts were made to carry the mixture of Diels-Alder products **124a** and **124b** forward so as to prepare a substrate for the oxa-di-π-methane rearrangement. Details are presented in Chapter 3.

2.3.2 Thermally-induced Diels-Alder reactions

Parallel to the work described in Section 2.3.1 another route to the non-natural enantiomer of 2-isocyanoallopupukeanane (*via* an intermolecular Diels-Alder reaction) was developed. The plan was to work on two slightly different but equally promising sequences and see how each would unfold. All efforts could then be concentrated on the more productive of the two at the appropriate point in time. There are two differences between the two approaches. First, the dienophiles used in the Diels-Alder reactions possess different EWGs – an aldehyde *vs.* a nitrile group. Furthermore, whereas the Diels-Alder product mentioned in Section 2.3.1 already carries a pendant chain in the position adjacent to the EWG, a similar chain has to be introduced, after the Diels-Alder step, onto the product of the alternative route described here.

The alternative pathway starts with a known and thermally-induced Diels-Alder cycloaddition reaction between acetonide-protected toluenediol derivative **70** and α-chloroacrylonitrile (**125**) (Scheme 2.16). This reaction is well-documented and provided an approximately 4:1 mixture of isomers **126a** and **126b**.[43] It was expected that further transformations of these materials would lead to a suitable photochemistry precursor. These transformations are discussed in detail in Chapter 3.

Scheme 2.16. Intermolecular Diels-Alder reaction with acrylonitrile **125**

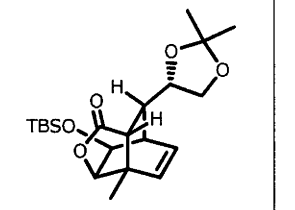


59 **70** **125** **126a** **126b**

Reagents and conditions: (a) *p*-TsOH·H_2O, DMP, 0°C, 2 h; (b) toluene, 92°C, 24 h.

2.4 Conclusions

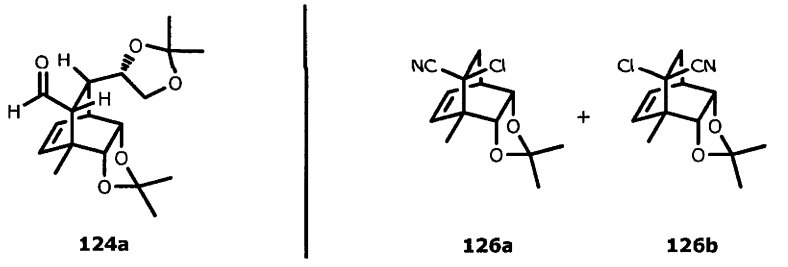
This Chapter has detailed work directed towards the first key-step of an anticipated synthetic route targeting the natural product 2-isocyanoallopupukeanane and its non-natural enantiomer. Unfortunately, the poor results obtained with the intramolecular Diels-Alder-based approach brought an end to such studies. Aside from a brief examination of the extent to which the intramolecular Diels-Alder product **105b** (Figure 2.6) could be further elaborated (see Section 3.2), this route was abandoned.



105b

Figure 2.6.

In contrast, more positive results were encountered with the equivalent intermolecular Diels-Alder reactions and these set a path towards the non-natural enantiomer of 2-isocyanoallopupukeanane. With the Diels-Alder products **124a** and **126a-b** in hand, explorations relating to the implementation of the second key-step – the oxa-di-π-methane rearrangement – could begin. Details of such work are presented in the following Chapter.



124a **126a** **126b**

Figure 2.7. *The intermolecular Diels-Alder products available for further elaboration*

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Chapter 3

Second key-step: the oxa-di-π-methane rearrangement

3.1 Introduction

The photochemical reaction that constitutes the second key-step in the present synthetic approach to 2-isocyanoallopupukeanane is an oxa-di-π-methane rearrangement, a reaction that involves *β,γ*-unsaturated carbonyl compounds as substrates and produces the isomeric cyclopropyl ketones as products.[1] The reaction usually proceeds *via* the triplet excited state, the production of which is promoted by a triplet sensitiser. Various mechanisms have been proposed for such conversions and the generally accepted one[2] is shown in Scheme 3.1 for reactions of the type presented herein. Thus, in the first step of the isomerisation biradical **128** is created. Fragmentation of the cyclopropane ring and regeneration of the carbonyl group within this species then delivers the new biradical **129** that "collapses" to give the observed product **130**.

Scheme 3.1. *Mechanism of the oxa-di-π-methane rearrangement*

127 **128** **129** **129** **130**

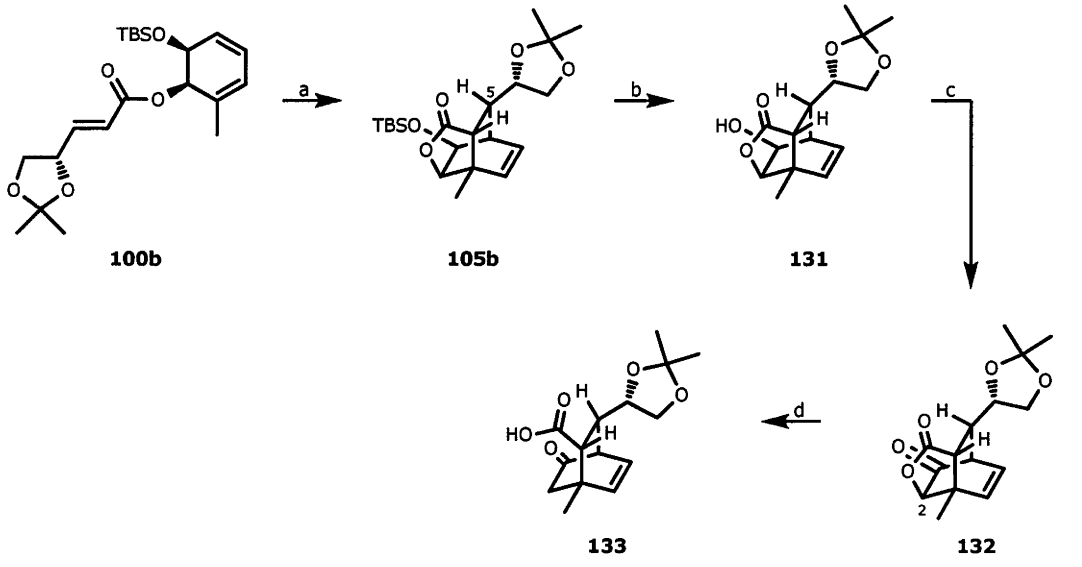
This Chapter deals with the elaboration of the Diels-Alder products – obtained as described in the preceding Chapter – to substrates that can participate in this photochemical rearrangement process. A brief description of the apparatus that has

been used for the irradiation process follows and the outcome of the successful photoreactions is then discussed.

3.2 Elaboration of intramolecular Diels-Alder adduct 105b

In order to explore the capacity for synthetic manipulation of various of the previously mentioned Diels-Alder adducts, the ester **100b** was subjected to an IMDA reaction thus generating the adduct **105b** in 84% yield. While this compound lacks the appropriate stereochemistry for implementation of the pivotal enolate alkylation reaction, it contains the functionalities that would allow for an exploration of the steps that might be necessary to generate substrates for the oxa-di-π-methane rearrangement (Scheme 3.2). The first manipulation of compound **105b**, namely removal of the TBS group, went smoothly, but the oxidation of the resulting alcohol **131** to ketone **132** was somewhat problematic. Thus, several conditions were evaluated but failed to produce useful yields of the desired ketone. Amongst these were the Bobbitt oxidation, the Swern oxidation, the use of IBX in DMSO and the use of 1.5 eq. of PCC. In a reaction with PDC, the molar equivalents of the reagent was increased to 5.0 and 4 Å molecular sieves were added.[3] This turned out to be the most successful approach, and desired ketone **132** was thereby obtained in 68% yield. However, expectations that treatment of ketone **132** with

Scheme 3.2. *Elaboration of Diels-Alder adduct **105b***



Reagents and conditions: (a) toluene, 120°C, 41 h; (b) TBAF, NH_4F, THF, 18°C, 0.75 h; (c) PDC, 4Å MS, CH_2Cl_2, 18°C, 4 h; (d) SmI_2, THF, MeOH, -78°C, 0.08 h.

SmI_2 would cause both the cleavage of the C-O bond at C2 and decarboxylation of the thus formed carboxylic acid proved optimistic. In the event, only the former reaction occurred, leading to carboxylic acid **133**. The illustrated structures of the compounds within the series were proven by X-ray analysis of adduct **132** (see Appendix A.1) and the sequence presented in Scheme 3.2 demonstrates that if the Diels-Alder product with the opposite, and thus desired, stereocentre at C5 could be generated, then a suitable photochemistry substrate could probably be obtained by such means. However, as noted in Chapter 2, attempts to prepare the desired Diels-Alder adduct **105a** had been problematic and efforts to obtain a photochemical substrate using this approach were much less effective than the ones involving an intermolecular Diels-Alder reaction. Therefore approaches of the type shown in Scheme 3.2 were abandoned and all efforts concentrated on implementing the synthetic plan starting from the products of the intermolecular Diels-Alder reactions described in Section 2.3 of the preceding Chapter.

3.3 Chemical elaboration of the intermolecular Diels-Alder product mixture 124a and 124b

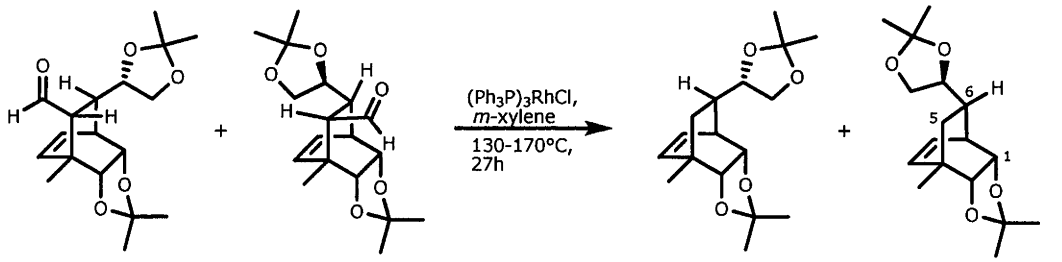
After the aldehyde group had fulfilled its purpose in activating dienophile **123** in the Diels-Alder cycloaddition reaction (Section 2.3.1, Page 38), it was no longer required and therefore its removal from Diels-Alder adducts **124a** and **124b** was investigated. Decarbonylation of aldehydes is commonly achieved using transition-metal catalysts based on rhodium and palladium.

$Rh(dppp)_2Cl$ is known as a mild agent for the decarbonylation of aldehydes,[4] but it is not readily available. A recent publication reports a convenient procedure for its *in situ* generation from $RhCl_3 \cdot 3H_2O$ and dppp in refluxing diglyme.[5] However, application of this method in the present case failed to yield decarbonylation products.

$[Rh(dppp)_2]^+BF_4^-$ is another rhodium-based catalyst that actively promotes the decarbonylation of aldehydes. However, it is not commercially available, and has to be prepared and then under the strict exclusion of air due to an otherwise ready incorporation of oxygen that renders the catalyst inactive.[6] After careful preparation of the catalyst from $Rh_2Cl_2(1,5\text{-cyclooctadiene})_2$, $AgBF_4$ and dppp, it was added to a solution of compounds **124a** and **124b** in *m*-xylene. As a consequence, product **134b** was isolated together with a hint of what is thought to be isomer **134a** (Scheme 3.3). The configuration of compound **134b** was determined using 1- and 2-D NMR spectroscopic techniques. Thus, a strong NOE correlation between H1 and

H6 helped to establish the configuration at C6. The absence of any significant quantities of decarbonylation product **134a** in the crude reaction mixture is surprising. Furthermore, the reaction did not go to completion and a considerable amount of starting material was recovered. Significantly, this was comprised almost exclusively of isomer **124b**.

Scheme 3.3. *Decarbonylation of a mixture of Diels-Alder adducts **124a** and **124b***



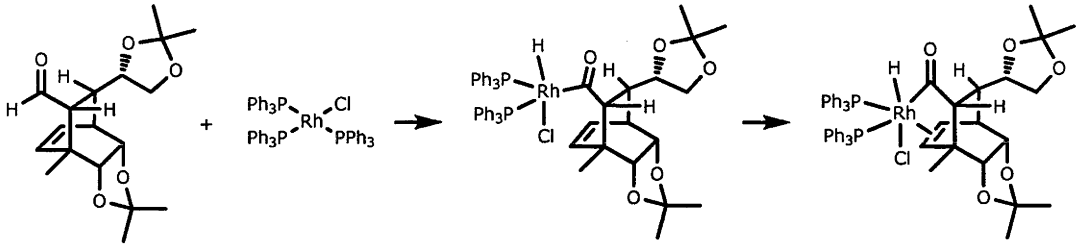
124a **124b** **134a** **134b**

Reagents and conditions: (a) $[Rh(dppp)_2]^+BF_4^-$, *m*-xylene, 140°C, 24 h or $(Ph_3P)_3RhCl$, *m*-xylene, 130-170°C, 27h.

Since the total amount of material recovered from the reaction described above was extremely low (29%, product to substrate ratio 1:3.7) and in order to see if low-quality catalyst was responsible for this situation, the reaction was repeated using a different rhodium-based reagent, namely $(Ph_3P)_3RhCl$ otherwise known as Wilkinson's catalyst.[7] This frequently used and commercially available reagent readily incorporates carbon monoxide during the decarbonylation process, and is thereby converted into the inactive species $(Ph_3P)_2(CO)RhCl$. As a consequence, stoichiometric amounts of the reagent are required. It has been shown that reactivity can be restored through the slow addition of a molar equivalent of diphenylphosphoryl azide (DPPA) to the reaction mixture.[8] However, to date this method has only been used in the decarbonylation of primary aldehydes which takes place at room temperature. Accordingly, isomers **124a** and **124b** were heated with a stoichiometric amount of $(Ph_3P)_3RhCl$ in *m*-xylene, thereby furnishing a product mixture that resembled the one obtained with $[Rh(dppp)_2]^+BF_4^-$. Even though the amount of isolated material was higher this time, the product was contaminated with a triphenylphosphine-containing species thereby preventing an accurate determination of yields. Once again, decarbonylation was incomplete and only product **134b**, traces of isomer **134a** and starting material **124b** could be isolated from the reaction mixture.

The lack of significant quantities of compounds **124a** and **134a** amongst the isolated components is attributed to the initially formed rhodium complex **136** (Scheme 3.4) interacting with the proximate double-bond and thus forming the π-complexed system **137**. A similar species has been suggested as an intermediate in rhodium-catalysed hydroacylation reactions, a transformation that occurs in olefins carrying an aldehyde functionality.[9,10] Further, some olefinic substrates appear to form especially strong bonds with $(Ph_3P)_3RhCl$.[11] A complex such as **137** could therefore be stable enough to prevent any further reaction. During the purification step this species would be expected to adhere to the top of a silica column, and hence not be detected amongst the elutants.

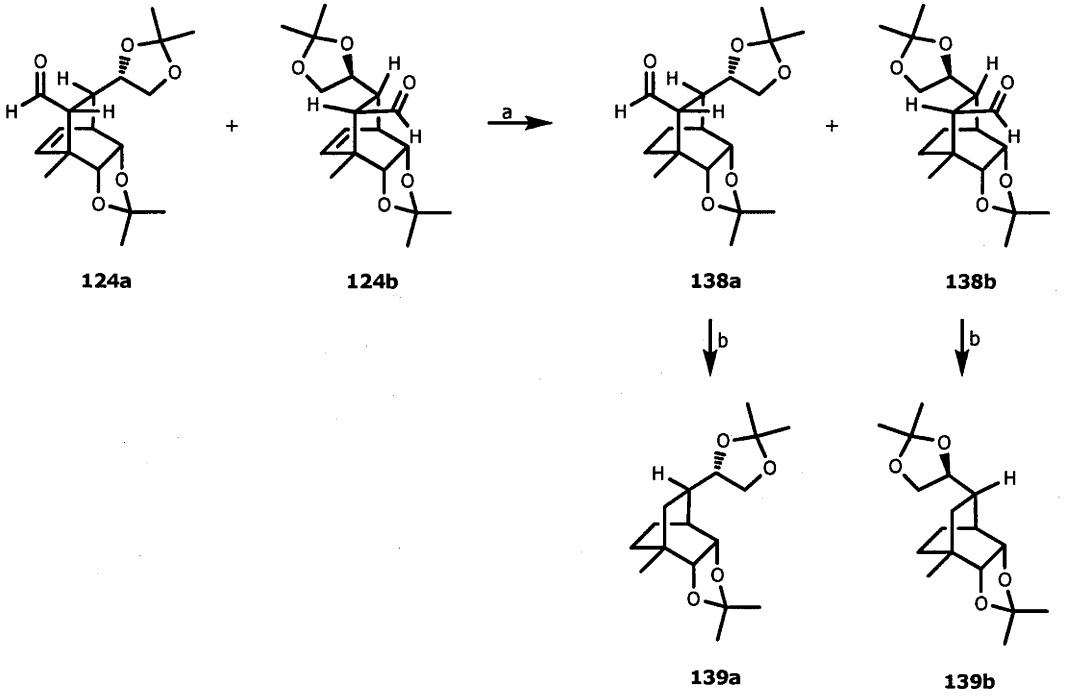
Scheme 3.4. *Simplified mechanism for the formation of rhodium complex **137***



124a **135** **136** **137**

To determine whether or not the rhodium catalyst does indeed interact with the double bond of compound **124a** in the fashion described above, the mixture of compounds **124a** and **124b** was subjected to hydrogenation (Scheme 3.5). The resulting saturated analogues **138a** and **138b** were separated by HPLC and both then successfully and independently decarbonylated with Wilkinson's catalyst. The reaction of each isomer proceeded somewhat sluggishly – after 2-3 days starting material could still be detected in both cases. More importantly, however, both decarbonylation products **139a** and **139b** were obtained and thus quite clearly indicating that the double bond within compound **124a** probably does interact with the catalyst and thus hinder decarbonylation within this system.

Scheme 3.5. *Reduction and decarbonylation of compounds **124a** and **124b***

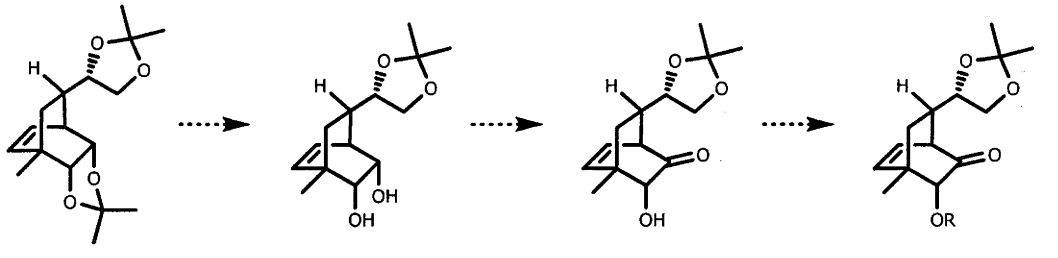


124a **124b** **138a** **138b** **139a** **139b**

Reagents and conditions: (a) H_2, Pd/C, EtOH, 18°C, 0.5 h; (b) $(Ph_3P)_3RhCl$, *m*-xylene, 130°C, 45-67 h.

This is as far as this area of research has been taken to date since deletion of the aldehyde group within compounds **124a** and **124b** clearly requires considerable effort. Provided the target olefin **134a** could eventually be obtained, then it could be elaborated to the target substrate **142** (Scheme 3.6), using well-established methodology that will be presented in more detail in Section 3.4.

Scheme 3.6. *Proposed pathway towards substrate **142** required for the oxa-di-π-methane rearrangement*



134a **140** **141** **142**

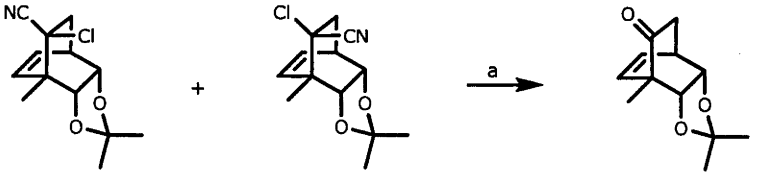
3.4 Further development of Diels-Alder adducts 126a and 126b

As the problems with the decarbonylation of adduct **124b** could not be readily resolved, work continued with the manipulation of Diels-Alder products **126a** and **126b**, the synthesis of which was described in Section 2.3.2 of Chapter 2 (page 39) and involved a facile intermolecular Diels-Alder reaction.

3.4.1 Synthesis of common building block 143

The synthesis of ketone **143** is well-documented[12] and proceeds through the Diels-Alder reaction between acetonide-protected toluenediol **70** and α-chloro-acrylonitrile (**125**) (Section 2.3.2) followed by the hydrolysis of the thus formed chloronitriles **126a** and **126b** with KOH in DMSO. The latter conditions were modified by Banwell *et al* to give improved yields of ketone **143**. Thus, treatment of chloronitriles **126a** and **126b** with ethanolic $Na_2S{\cdot}9H_2O$,[13,14] gave compound **143** cleanly and in up to 70% yield (Scheme 3.7).[15]

Scheme 3.7. *Preparation of general precursor* ***143***



126a **126b** **143**

Reagents and conditions: (a) $Na_2S{\cdot}9H_2O$, EtOH, 92°C, 15 h.

Ketone **143** was the substrate used in all of the synthetic work presented from this point onwards. Sections 3.4.2, 3.4.3 and 3.4.5 describe different efforts to convert this pivotal compound into a species suitable for participation in the oxa-di-π-methane rearrangement.

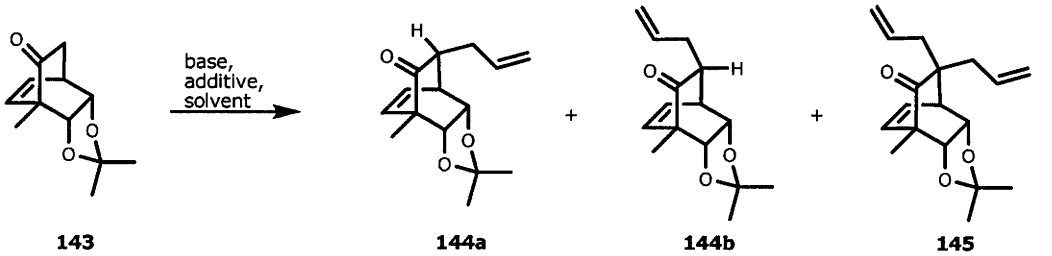
3.4.2 Allylation of ketone 143

With ketone **143** in hand, methods for its conversion into a substrate suitable for the oxa-di-π-methane rearrangement were explored. The first task was the introduction of a side-chain adjacent to the carbonyl group. For this purpose, a moiety that can be easily transformed into the required vicinal-diol unit was sought. Initially the choice fell on an allyl group as it was expected that allylic oxidation followed by cleavage of the double bond would bring about the formation of an α-hydroxyaldehyde. Reduction of the aldehyde functionality within the latter would then provide the required diol.

In an effort to prepare the required allylated compound, one equivalent of allyl bromide was slowly added to the enolate anion derived from ketone **143**. This resulted in a mixture of three products, namely the two epimeric monoallylated adducts, *viz.* compounds **144a** and **144b**, and the *bis*-allylated analogue **145** (Scheme 3.8). The structure of adduct **144a** was confirmed by X-ray crystallography (see Appendix A.2). The conditions favoured the formation of monoallylated compound **144b** while the desired product, **144a**, with the allyl group situated "above" the acetonide group, was only obtained in very small amount.

Another major drawback of this approach was that a significant amount of starting material was recovered from the allylation reaction. On the other hand, the addition of more than one equivalent of allyl bromide to the reaction mixture increased the amount of *bis*-allylated component **145** significantly. The results shown in Table 3.1 reveal that variation of the base and the use of TMEDA as an additive do not significantly alter the ratio* of the products.

Scheme 3.8. *Outcomes from the α-allylation of ketone* ***143***



143 **144a** **144b** **145**

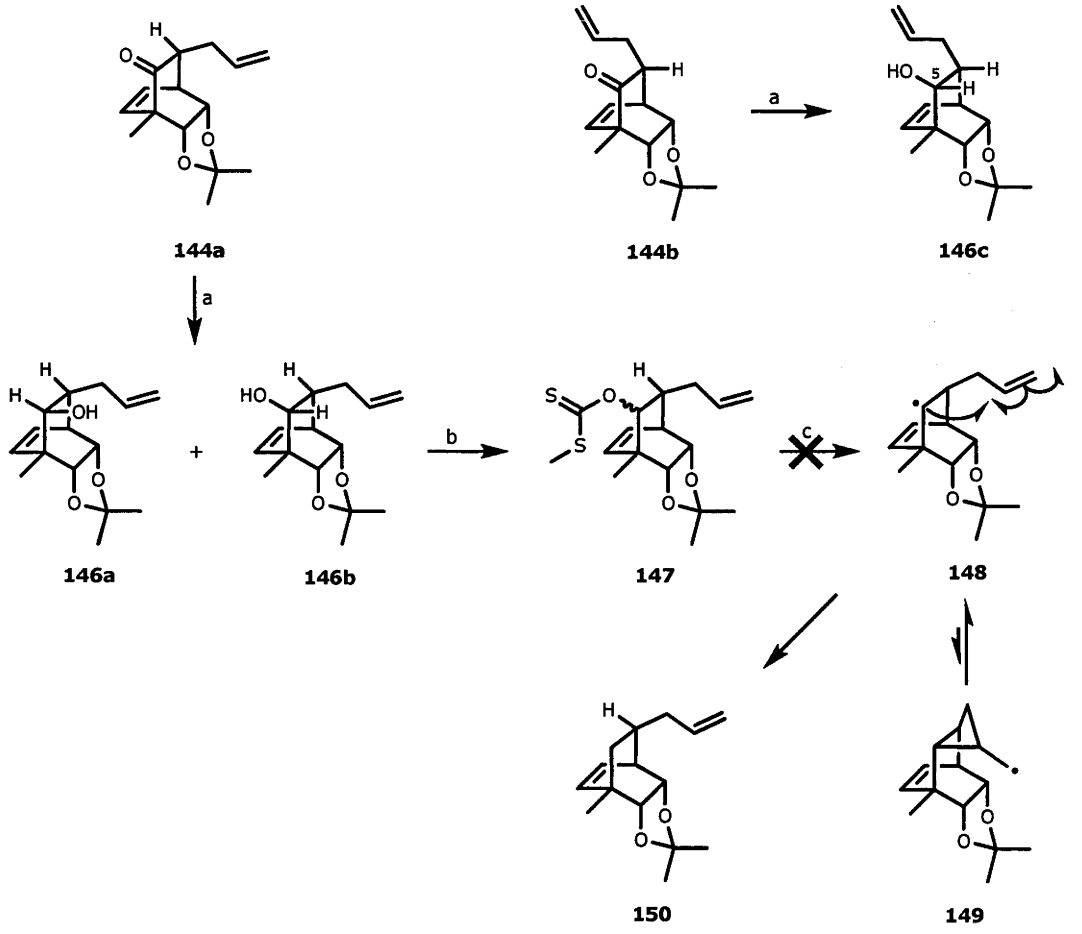
Table 3.1

Reagents and conditions	143	144a	144b	145
LDA, allyl bromide, THF, -78°C→0°C→18°C, 20 h	4.2	1	5.9	2.4
LDA, TMEDA, allyl bromide, THF, -78°C→0°C→18°C, 18 h	5.4	1	6.7	1.8
LiHMDS, allyl bromide, THF, ether, -78°C→0°C→18°C, 33 h	-	1	4.3	2.1
NaH, allyl bromide, THF, 80°C, 8 h	3.8	1	5.4	4.6

* Ratios were calculated from the integrals of relevant peaks in a ^{1}H NMR spectrum of the crude product

A short study was conducted on how the monoallylation products might be manipulated chemically for the purposes of obtaining a substrate for the photochemical reaction. Accordingly, removal of the carbonyl group was attempted through a sequence involving initial reduction then elimination of the resulting hydroxy group. Thus, monoallylated ketones **144a** and **144b** were separately treated with $NaBH_4$ and thereby yielding alcohols **146a-c**[†] (Scheme 3.9). The structure of the last of these was determined by X-ray analysis (Figure 3.1). Deoxygenation of the mixture of alcohols **146a** and **146b** was attempted using the Barton-McCombie protocol.[16] The crude product arising from the attempts to convert these alcohols into the corresponding xanthate esters afforded a 1:2.5 mixture of the starting materials and the epimeric forms of derivative **147**. Treatment of the latter pair of compounds with tri-*n*-butyltin hydride was expected

Scheme 3.9. *Attempted removal of the ketone unit within compounds **144a** and **144b***



Reagents and conditions: (a) $NaBH_4$, EtOH, 0°C→18°C, 5.5-17 h; (b) i. NaHMDS, THF, 0°C→18°C, 1.5 h; ii. CS_2, 18°C, 2 h; iii. MeI, 0°C→18°C, 4 h; (c) n-BuSnH, AIBN, toluene, 120°C, 20 h.

[†] Reduction of ketone **144b** yielded alcohol **146c** together with a small fraction of its C5 epimer the first time the reaction was carried out. When the reaction was repeated, only alcohol **146c** was obtained.

to lead to reduction product **150**. While cyclisation of the derived radical **148** *via* a 4-exo-trig process is possible, this was not observed in another, similar, system.[17] Moreover, a kinetic study of pentenyl and (cyclobutyl)methyl radicals shows that the ring-opened product is strongly favoured.[18,19] Accordingly, it was considered that the most likely end-product of the reduction process would be the desired compound **150**. In the event, however, this compound was not obtained. Only the starting materials were recovered. The inability to effect the desired reduction cannot be explained at this point.

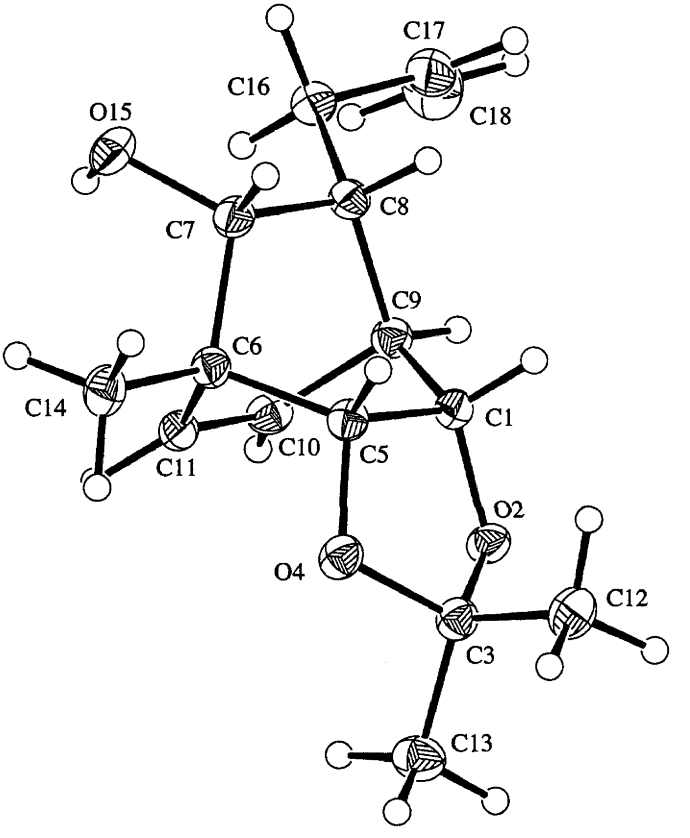


Figure 3.1. *ORTEP derived from the single-crystal X-ray analysis of compound **146c**.*

The outcomes defined above clearly indicate that monoallylation of ketone **143** is extremely difficult to achieve. Furthermore, the undesired epimer **144b** forms much more readily than the required one (**144a**). Since the LiHMDS-catalysed epimerisation of compound **144b** to **144a** was very sluggish (and the best result gave a 3.6:1 mixture in favour of the undesired isomer) a new means for introducing the side-unit was required. Details of this are presented in the following Section.

3.4.3 Acylation of ketone 143

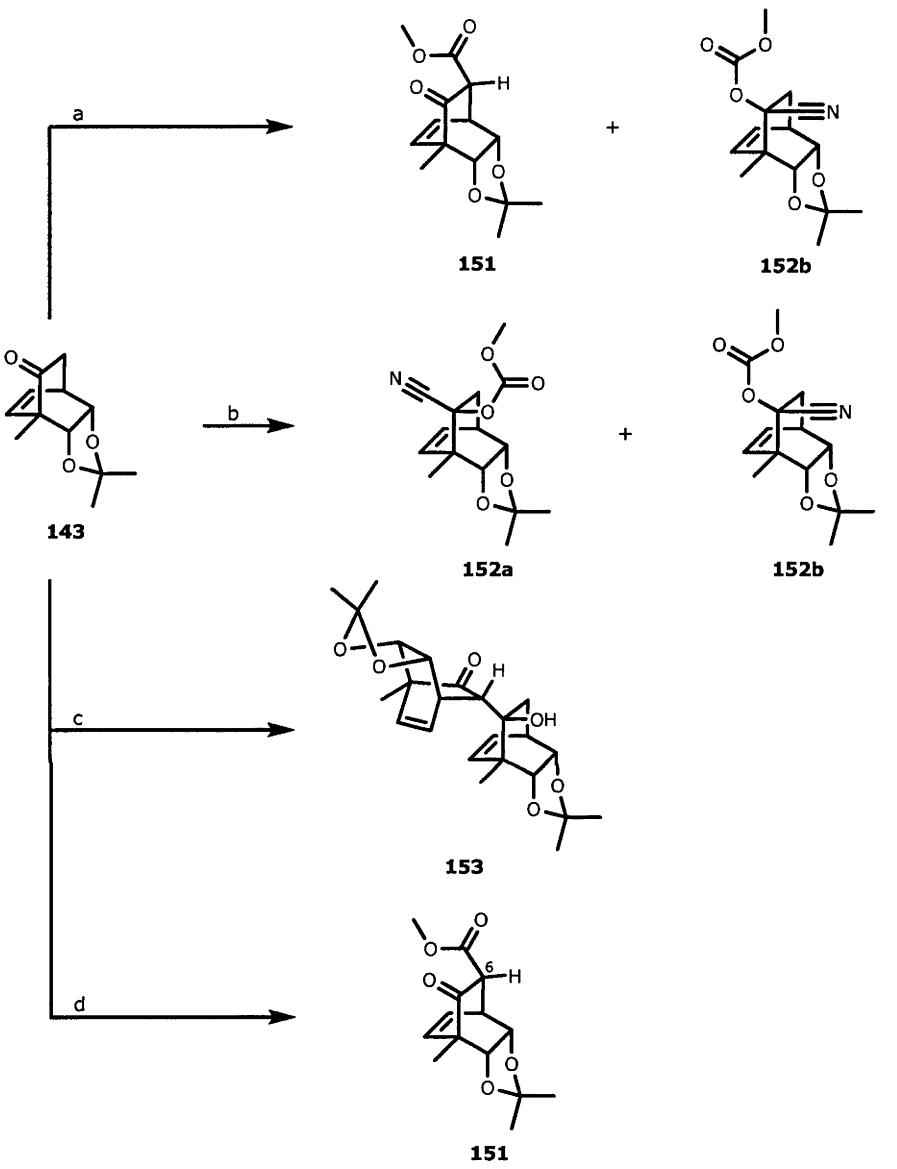
Ketone **143** was converted into the corresponding enolate in the same way as described in the previous Section and then reacted with methyl cyanoformate (Mander's reagent[20]) rather than allyl bromide. A *β*-ketoester was expected as the major product. However, a range of product mixtures was obtained depending upon the precise reaction conditions employed (Scheme 3.10). In an effort to refine matters, and following previously published conditions[21], one equivalent of ketone **143** in diethyl ether was treated with 1.5 equivalents of LiHMDS in THF and ten equivalents of Mander's reagent (Scheme 3.10, condition a). After 1.8 hours at ambient temperatures, a mixture containing mainly the *C*-acylated product **151** and cyanohydrin carbonate **152b**, as well as small amounts of their respective epimers, was isolated. The structure of compound **152b** was confirmed by X-ray crystallography (Figure 3.2). Even though enol carbonate formation is known to compete with *C*-acylation processes during reactions involving cyanoformates, the formation of a cyanohydrin carbonate was unexpected although there are some precedents.[22] When the reaction was repeated with 1.5 equivalents of LiHMDS in THF and just 1.1 equivalents of Mander's reagent, then the reaction slowed down considerably. Thus, after stirring at room temperature for 19 days, a mixture of *O*-acylated products **152a** and **152b** was observed (Scheme 3.10, condition b).

It has been shown that *O*-acylation can be suppressed by using ether rather than THF as solvent.[23] The reaction was, therefore, repeated in the exact same manner as above (using 10 equivalents of Mander's reagent), but with a solution of LiHMDS in hexane (Scheme 3.10, condition c). The result was a reaction that gave a mixture of small amounts of *C*- and *O*-acylation products, and a new and major component, namely the aldol condensation product **153**. The structure of this last compound was established by single crystal X-ray analysis (Figure 3.3).

The fact that switching solvents alone did not eliminate the formation of side products prompted a reinvestigation of the acylation method. The publication that reports on the formation of cyanohydrin carbonates contained a description of a study on the outcomes of these sorts of reactions at different temperatures. It was found that the *O*-acylation process proceeds smoothly at 0°C and 20°C, while none of the carbonate forms at very low temperatures such as -78°C.[22] In keeping with this report, when two equivalents of each of LiHMDS (in THF) and Mander's reagent were used, and the reaction temperature kept at –78°C then the *C*-acylation product **151** was obtained in 67% yield (Scheme 3.10, condition d). The structure of *β*-ketoester **151** was established using 1- and 2-D NMR spectroscopic techniques. Even though the configuration at C6 is opposite to that required,

compound **151** was elaborated further on the basis that an epimerisation process could eventually be used to establish the required stereochemistry at this centre.

Scheme 3.10. *Acylation reactions of ketone **143** with Mander's reagent*



Reagents and conditions: (a) i. LiHMDS, Et_2O, THF, 0°C, 3 h; ii. NCCOOMe, -78→18°C, 2.2 h; (b) i. LiHMDS, Et_2O, THF, -78°C, 2.25 h; ii. NCCOOMe, -78→18°C, 19 days; (c) i. LiHMDS, Et_2O, hexane, 0°C, 2.7 h; ii. NCCOOMe, -78°C→0°C→18°C, 2.2 h; (d) i. LiHMDS, Et_2O, THF, -78°C, 3.3 h; ii. NCCOOMe, -78°C, 5.7 h.

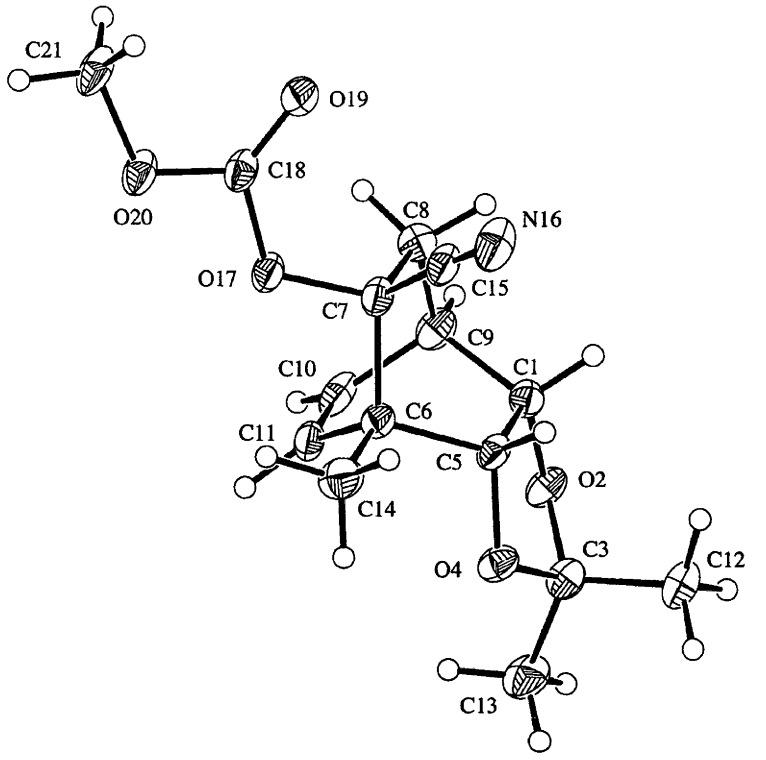


Figure 3.2. *ORTEP derived from the single-crystal X-ray analysis of compound **152b***

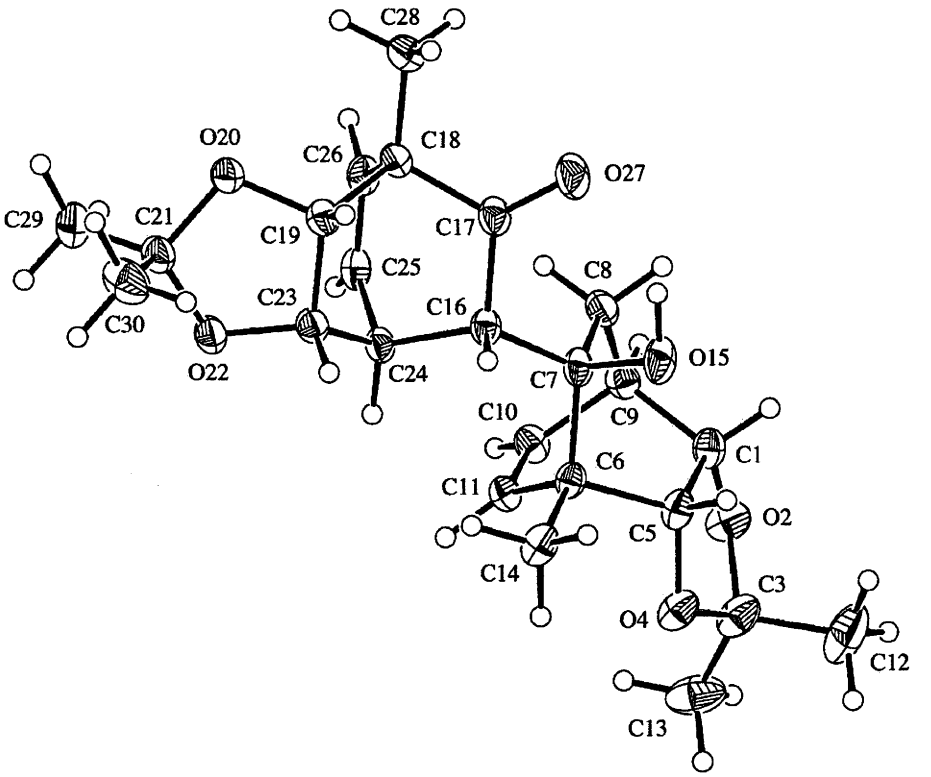


Figure 3.3. *ORTEP derived from the single-crystal X-ray analysis of compound **153***

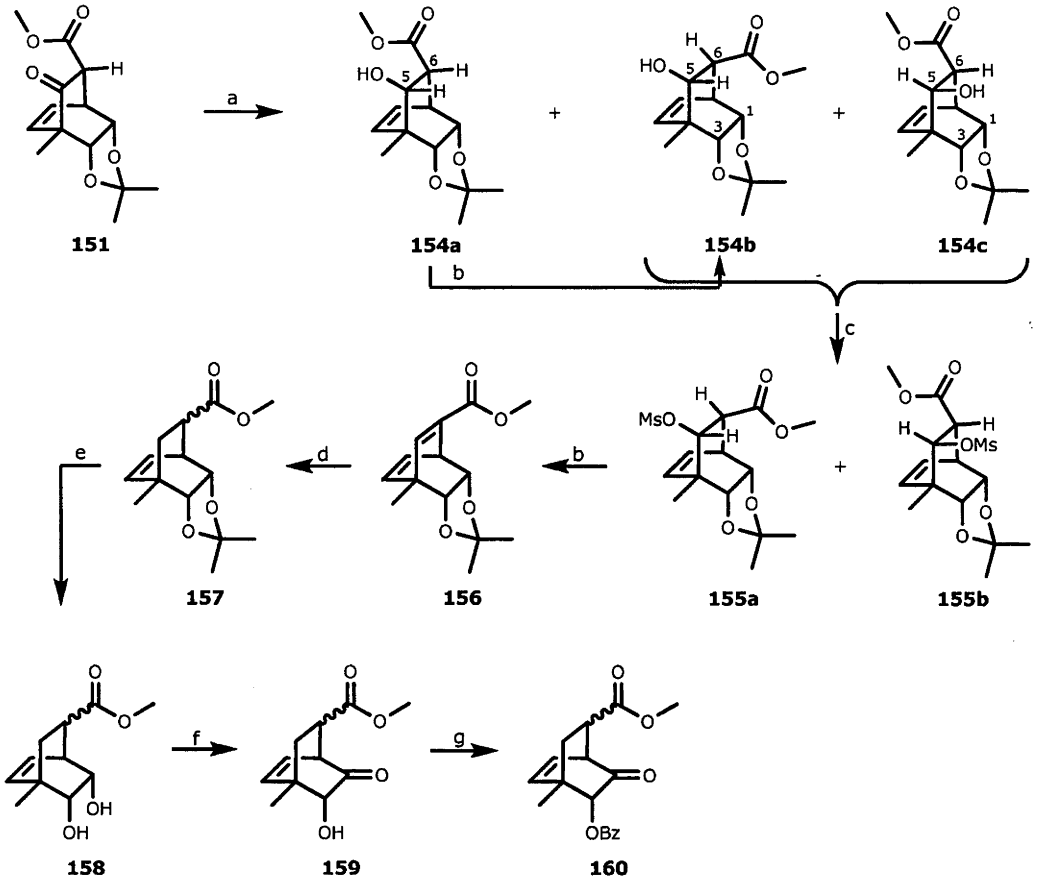
Thus, the synthetic route continued with the reduction of the ketone group on β-ketoester **151** using $NaBH_4$, a reaction that afforded three products, namely the stereoisomeric β-hydroxyesters **154a-c** in 82% yield and with a *cis*:*trans*-adduct ratio of 2.4:1 (Scheme 3.11). The *cis*- or *trans*-relationship between the hydroxy and the ester group in these three compounds was determined through inspection of the vicinal coupling between the signals due to the protons on C5 and C6. While the ^1H NMR spectrum of compound **154a** exhibits signals that can be used to assign a *cis*-relationship ($J_{5,6}$ = 8.5 Hz), the corresponding spectra of compounds **154b** and **154c** show signals where $J_{5,6}$ = 3.5-4.0 Hz, and thus suggesting a *trans*-relationship between the relevant groups. These last two compounds were distinguished from one another by considering the NOE's between the signals due to the protons on C1, C3, C5 and C6. In addition, the structure of one of the *trans*-alcohols (**154b**) could be confirmed by X-ray crystallography (see Appendix A.6).

Several attempts were made to find reducing conditions that suppress the formation of *cis*-product **154a** as this does not take part in the subsequent elimination sequence described below. However, reduction of the ketone moiety within β-ketoester **151** with Luche's reagent only led to the formation of *cis*-β-hydroxyester **154a**, while the use of L-selectride failed to give any reaction at all.

In an effort to effect the elimination of the elements of water within these reduction products, a mixture of compounds **154a-c** was subjected to treatment with mesyl chloride and the products so-formed then heated with DBU. However, only the *trans*-alcohols **154b** and **154c** participated in the mesylation reaction and, after the elimination step, contributed to the production of the doubly unsaturated ester **156**. *cis*-Alcohol **154a** remained inert towards mesylation, a situation that can be attributed to steric effects exerted by the adjacent ester group. However, the same compound was found to epimerise to *trans*-isomer **154b** on treatment with DBU. Thus, epimerisation of alcohol **154a** in the presence of DBU gave an approximately 1:3.4 mixture of β-hydroxyesters **154a** and **154b**. The latter was then treated in the manner describe above so as to provide additional quantities of compound **156**.

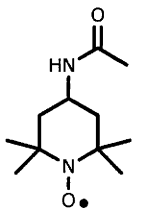
The next task was to find suitable conditions that would selectively reduce the conjugated double bond in compound **156** without affecting the unconjugated one. The required chemoselectivity has been achieved previously (in other systems) using $NaBH_4$ in methanol/THF.[24] Application of these conditions to compound **156** afforded a *ca.* 1:1 mixture of the diastereomeric forms of compound **157** in 81% yield. Since the two product isomers were slightly difficult to separate they were committed to the next step as a mixture.

Scheme 3.11. *Synthesis of the photochemistry precursor* ***160***

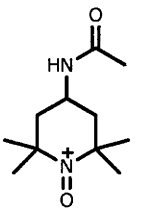


Reagents and conditions: (a) $NaBH_4$, EtOH, 0°C→18°C, 1.5 h; (b) DBU, benzene, 70-72°C, 15-21 h; (c) MsCl, Et_3N, CH_2Cl_2, 0°C→18°C, 5 h; (d) $NaBH_4$, MeOH, THF, 0°C→18°C, 4.5 h; (e) DOWEX-50, MeOH, H_2O, 100°C, 20 h; (f) *p*-TsOH·H_2O, 4-AcNH-TEMPO, CH_2Cl_2, 0°C→18°C, 23 h; (g) BzCl, Et_3N, DMAP, CH_2Cl_2, 0°C→18°C, 20 h.

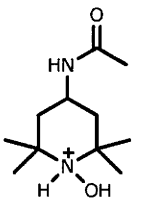
Acid-promoted deprotection of the acetonide group within compound **157** was carried out with activated DOWEX-50 in aqueous methanol at reflux.[25] The epimeric mixture of diols **158** formed in this way was then selectively oxidised to give the corresponding acyloins (**159**) using the sterically demanding oxoammonium salt derived from 4-acetamido-TEMPO (**161**) (Figure 3.4).[26] Nitroxide **161** forms oxoammonium salt **162** *in situ* upon treatment with acid, such as the *p*-TsOH used in the present case. During oxidation of the alcohol group(s) the oxoammonium salt is consumed, and reduced to hydroxylamine salt **163** that precipitates from the solution. The steric bulk of this reagent results in the more accessible hydroxy group on the diols being oxidised exclusively when one molar equivalent of the reagent is used.[27]



4-AcNH-TEMPO (**161**)



oxoammonium salt **162**



hydroxylamine salt **163**

Figure 3.4.

With acyloin **159**‡ in hand, the stage was almost set for the oxa-di-π-methane rearrangement step. Only one further chemical step needed to be carried out, namely protection of the free hydroxy group within acyloin **159**. Protection was seen as necessary as previous efforts to subject a related acyloin to an oxa-di-π-methane rearrangement have lead to mixtures of dimers.[28] The choice fell on the benzoyl group as it has already proved itself during related photochemical processes.[25] The epimeric forms of the photochemical substrate **160**§ thereby obtained were separated chromatographically and each independently subjected to the photochemistry step.

Even though compound **160** had now been obtained, the route leading to it was rather lengthy. Accordingly, various attempts were made to improve access to this compound. These are described in the following Sections.

3.4.3.1 Alternative routes to adduct 156

As noted in Section 3.4.3, dehydration of *cis*-alcohol **154a** to form the unsaturated ester **156** proved somewhat problematic. Even though the former compound could be efficiently epimerised to the *trans*-isomer **154b** and this then dehydrated, its direct conversion into olefin **156** would be preferable since this would reduce the total number of synthetic steps leading to the substrate for the photochemical rearrangement reaction. To such ends, the dehydration of compound **154** using acidic conditions was investigated. Thus, a mixture of alcohols **154a-c** was treated

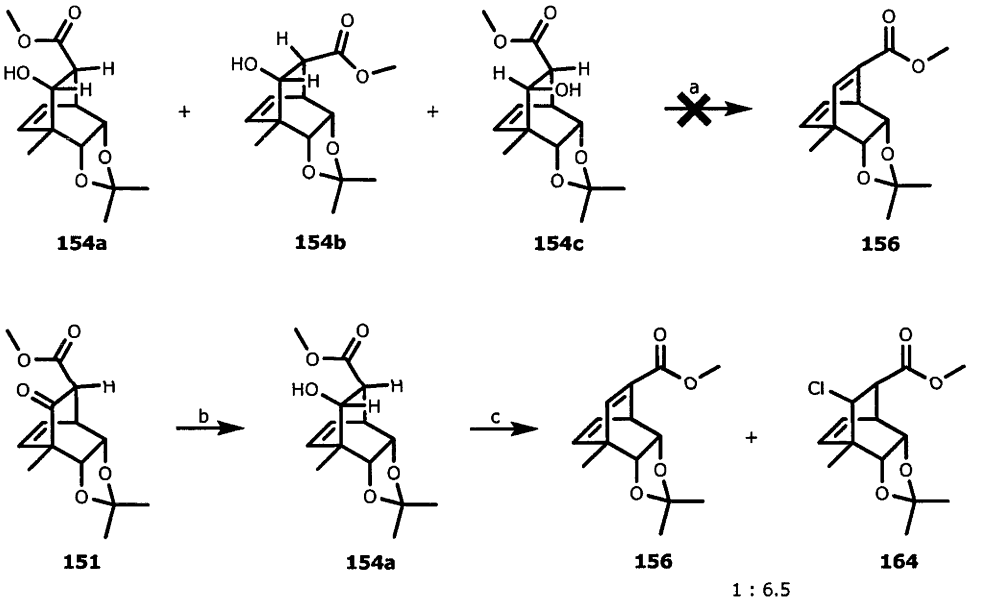
‡ The two isomers of compound **159** were chromatographically inseparable. On the other hand, the benzoyl protected isomers **160** were chromatographically separable. A sample of each isomer of **160** was separately deprotected with scandium triflate, a reagent that cleaves ester groups without causing epimerization (see Demir, A. S.; Sesenoglu, O. *Organic Letters* **2002**, *4*, 2021). The reaction was not very efficient, but gave enough material for the full characterization of the two acyloins.

§ The structure of one of the epimeric benzoates (**160a**) was confirmed by X-ray crystallography (see Appendix A.7).

with *p*-TsOH in refluxing benzene or toluene in an apparatus connected to a Dean-Stark trap (Scheme 3.12). However, under such conditions no reaction took place.

Another attempt at dehydration involved treatment of alcohol **154a** with thionyl chloride in pyridine.[29] A mixture of products was thereby obtained but only two of them could be isolated and then as an inseparable 1:6.5 mixture and in *ca.* 23% combined yield. The desired product **156** made up the minor component therein, while the other was assumed to be chlorinated product **164**. Removal of the chlorine was considered but ultimately dismissed as the application of such protocols would not have reduced the number of steps.

Scheme 3.12. *Alternative procedures for the preparation of ester **156***



Reagents and conditions: (a) *p*-TsOH, benzene (80°C) or toluene (120°C), Dean-Stark trap, 24 h; (b) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0°C→20°C, 24 h; (c) $SOCl_2$, pyridine, 18°C, 34 h.

Given these deficiencies, another route, this time directed towards acquiring compound **157**, was explored. Details are provided in the following Section.

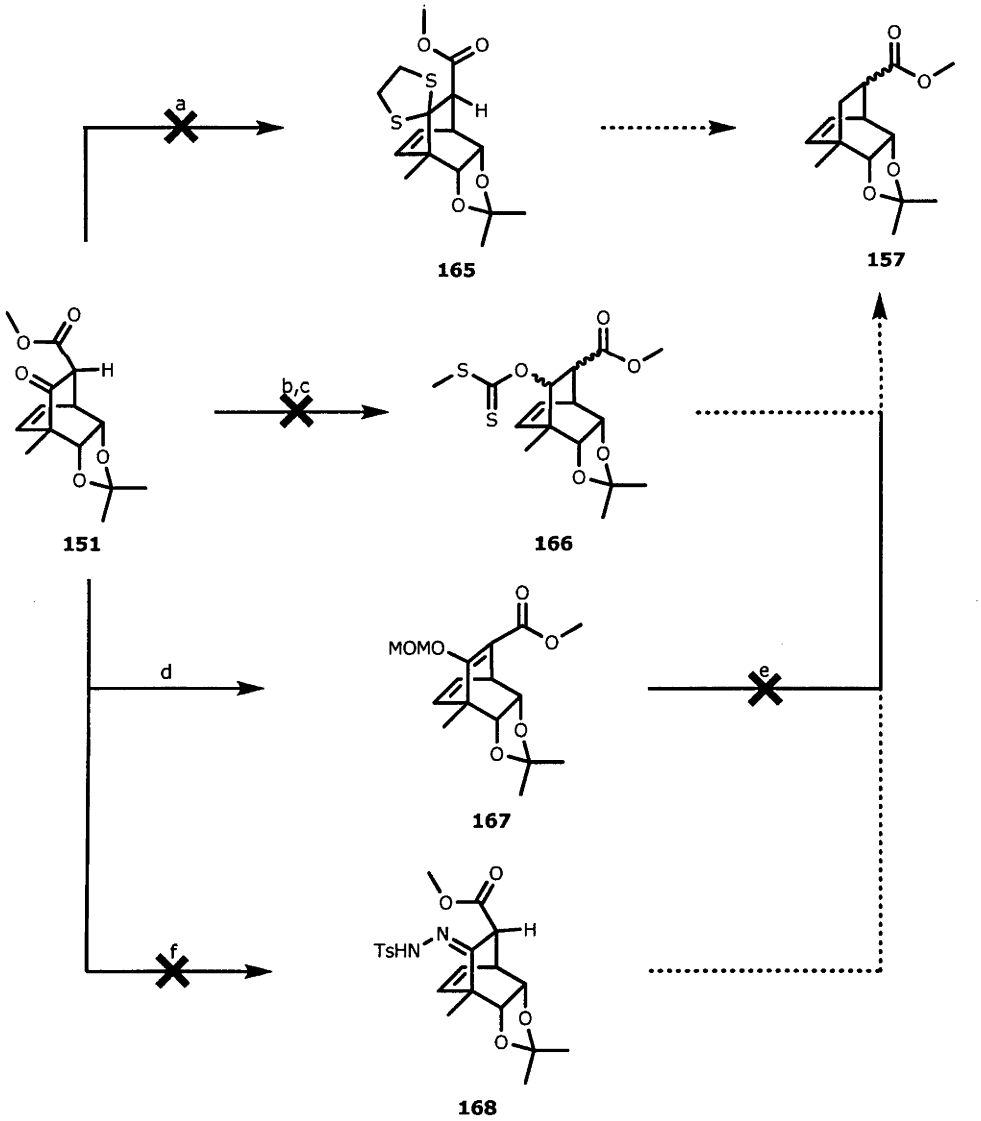
3.4.3.2 Alternative routes to adduct 157

Various methods were examined in an effort to delete the keto group associated with compound **151** in a more direct manner than detailed in Section 3.4.3. Such an approach, if successful, would bypass the reduction/epimerisation/elimination sequence discussed earlier and thereby reduce the number of synthetic steps.

Accordingly, ester **151** was treated with ethanedithiol and $BF_3{\cdot}Et_2O$ in an effort to prepare thioketal **165**. Desulfurisation of the latter with Raney Nickel was then expected to give access to ester **157** (Scheme 3.13). However, the implementation of such a plan was thwarted because the desired thioketal **165** could not be formed under these or other related conditions.

The next approach involved reduction of the ketone group and subsequent deoxygenation of the newly formed alcohol group, using the Barton-McCombie protocol.[16] Unfortunately, the preparation of the required xanthate ester **166** from the precursor alcohols **154a-c** failed. Only the elimination product **156** was isolated under the relevant conditions and then only in very low yield.

Scheme 3.13. *Alternative procedures for the preparation of ester **157***



Reagents and conditions: (a) $HS(CH_2)_2SH$, $BF_3{\cdot}Et_2O$ or $InCl_3$, CH_2Cl_2, 18°C, 24 h; (b) $NaBH_4$, EtOH, 0°C→18°C, 1.5 h; (c) i. NaHMDS, THF, 0°C→18°C, 2 h; ii. CS_2, 0°C→18°C, 2 h; iii. MeI, 0°C→18°C, 4.5 h; (d) NaH, MOMCl, DMPU, 0°C→18°C, 3 h; (e) Li/NH_3, Et_2O, -78°C→-33°C, 0.5 h; (f) *p*-$TsNHNH_2$, EtOH, 85°C, 16 h.

In another attempt to prepare target **157**, β-ketoester **151** was to be transformed into the methoxymethyl enol ether **167** which would then be treated with lithium in liquid ammonia in an attempt to effect reduction[30] of the enol ether to ester **157**. In the event, treatment of compound **151** with base and chloromethyl methyl ether in DMPU (as solvent) gave *O*-alkylation product **167** relatively cleanly and the latter was then subjected to dissolving metal reduction. However, only a very small amount of the expected product was obtained as part of a complex mixture. Furthermore, the reaction conditions used caused reduction of the ester moiety to an alcohol.

The last attempt to establish an improved synthesis of ester **157** consisted of the conversion of β-ketoester **151** into tosylhydrazone **168**, followed by treatment of this species with sodium cyanoborohydride.[31,32] A compound reminiscent of the tosylhydrazone was observed in the product mixture derived from the first step of this sequence. The reaction was, however, very sluggish and only partial conversion had taken place after 16 h, making it unattractive to continue along this path.

Due to the less than acceptable results obtained through the investigations detailed in this Section, further attempts to refine the synthesis of ester **157** were abandoned. Instead, attention was turned towards the photochemical rearrangement of compound **160** as described in the next Section.

3.4.4 The oxa-di-π-methane rearrangement

The pivotal oxa-di-π-methane rearrangements of compounds **160a** and **160b** were carried out according to a previously published method, namely using acetone as the solvent and acetophenone as the triplet sensitiser.[25,33] Two different "set-ups" were available to carry out the transformations (Figure 3.5). Initially system (a) was used. This consisted of a Pyrex reaction vessel lowered into a beaker containing a filter solution, specifically an aqueous solution of NaBr and $Pb(NO_3)_2$. The beaker was, in turn, placed in a basin that served as a cooling bath for the reaction. The high-pressure mercury lamp (a Philips 125 W HPL-N lamp) sat in its own cooling jacket that was attached, in a vertical orientation, to the outside of the reaction cooling bath.

System (b) depicts a newer system that was acquired (and used) at a later stage. This quartz immersion well photoreactor (ex. Ace Glass Inc.) was equipped with a Pyrex filter that was eased along the inside of the lamp cavity of the cooling jacket. The reaction mixture was subjected to irradiation with a medium pressure quartz mercury-vapour lamp (a 450W Hanovia lamp) but was not cooled separately in this case.

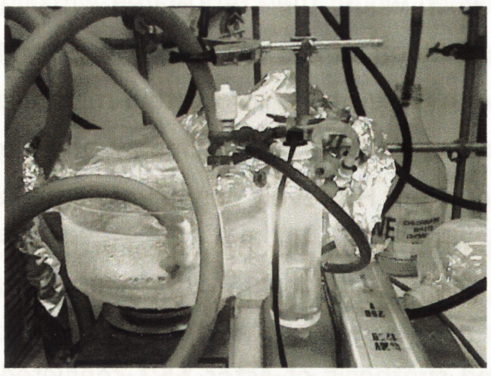
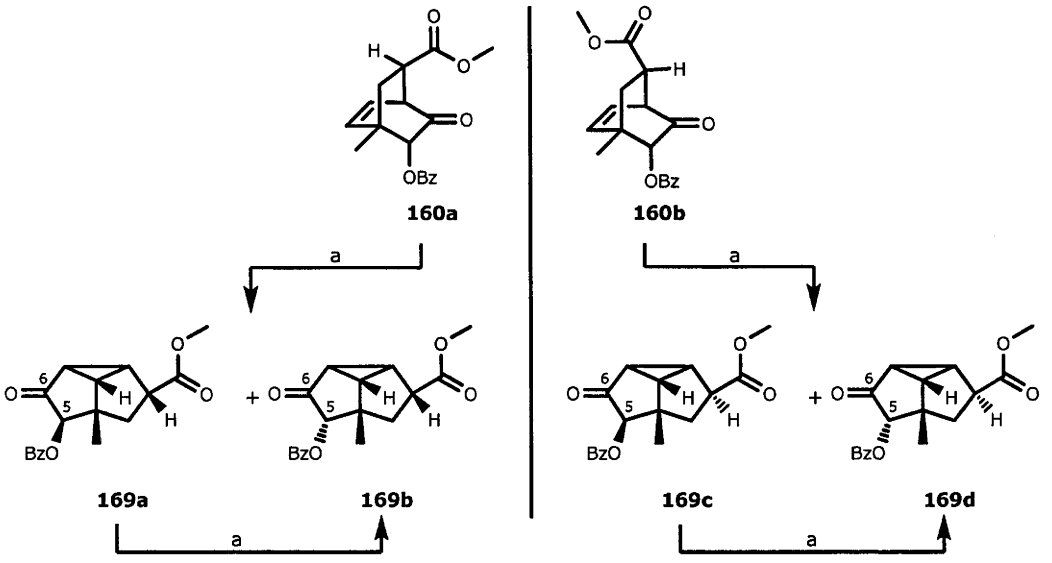


Figure 3.5. *Two different photoreactors used for effecting the oxa-di-π-methane rearrangements of compounds* ***160a*** *and* ***160b***

There were some differences between the two systems. System (a) had a relatively small lamp, which meant that reactions took 2-3 days. On the other hand, due to the lamp size this set-up was "less harsh" and thus leading to an exceptionally clean reaction and, therefore, high yields of the desired product. One disadvantage of such a set-up is that the reaction only occurs in immediate proximity to the lamp. Accordingly, the size of the reaction vessel was restricted by the length of the lamp which was only a few centimetres long. Due to the additional demands for high dilution (*ca.* 200 ml solvent per mmol substrate) that had been found necessary to effect the rearrangement in high yield,[25] only small batches of starting material could be processed at any one time. As a consequence, the combination of high dilution and relatively long reaction times meant that the conversion of gram quantities of starting material into photoproduct took weeks to carry out.

System (b) was much more efficient in this respect, with reactor volumes of up to 1000 ml being attainable. Accordingly, large quantities of substrate could be converted in this new reactor, and the more powerful lamp reduced reaction times to a few hours. On the other hand, the crude product consisted of more components/decomposition products and proved more difficult to purify due to the harsher conditions being employed. This 'problem' was, however, rather insignificant compared to the time that could be saved by using this reactor.Irradiation under the above mentioned conditions caused a triplet-sensitised reaction and the independently treated isomers **160a** and **160b** each gave two products in 70% combined yield (Scheme 3.14).** In keeping with observations made on related systems, the ratio of the products varies with reaction time.[25] At the start of the reaction, diquinanes **169a** and **169c** prevail in the corresponding reaction mixtures. However, upon using longer irradiation times, epimerisation of the benzoyloxy group at C5 resulted in the accumulation of isomers **169b** and **169d**, respectively. This secondary isomerisation process could proceed *via* a photoenolisation process[34] or involve photolytic cleavage of the bond between C5 and C6 (a Norrish type I reaction), to give a diradical that, after intersystem crossing, recombines to give a mixture of epimers. The driving force for the epimerisation of adducts **169a** and **169c** is probably the removal of torsional strain between the adjacent and *syn*-related benzoyloxy and methyl groups.

Scheme 3.14. *Outcomes of the oxa-di-π-methane rearrangement reactions of photosubstrates **160a** and **160b***



Reagents and conditions: (a) acetophenone, acetone, hv, 5-15°C, 3 h to 3 days.

** The structure of diquinane **169a** was confirmed by X-ray crystallography (see Appendix A.8).

The acquisition of diquinanes **169a-d** completed the second pivotal stage of the proposed route to the tricyclic framework of 2-isocyanoallopupukeanane. However, even though useful photoproducts had been prepared, the efficiency of the route was not optimal. A relatively small amount of material was available to continue towards the last key step and the final target molecule. Nevertheless, the already obtained photoproducts **169a-d** were taken further towards the intramolecular alkylation key-step, as depicted in the next Chapter. Alongside this, however, work on a slightly different route was begun in an attempt to make the synthetic sequence leading to the substrate for the photochemical rearrangement more efficient. Relevant studies are described in the following Section.

3.4.5 Modification of the original route

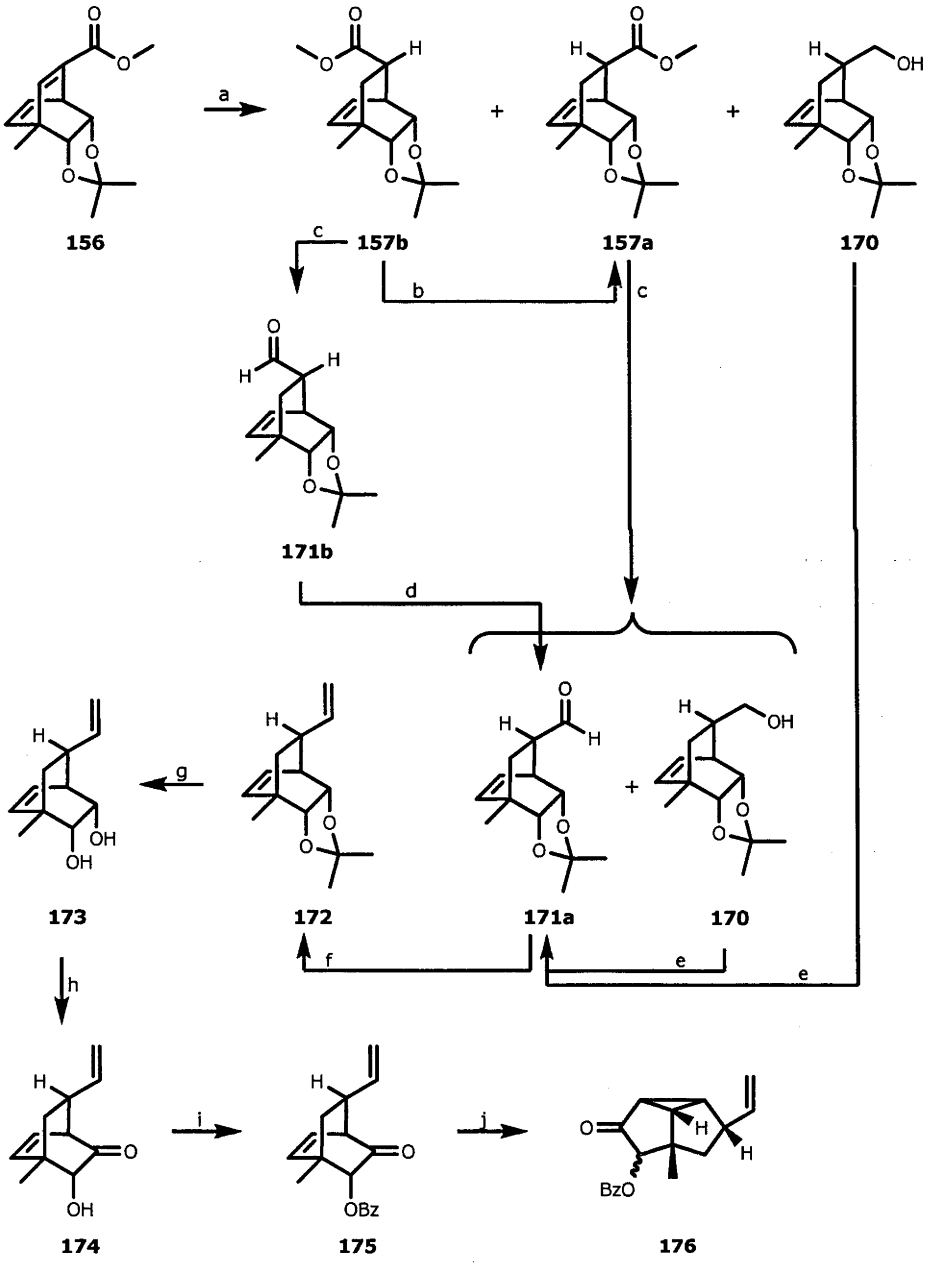
Parallel to the pursuit of the route depicted in Section 3.4.3, a different pathway that branches off from ester **157** was explored (Scheme 3.15) in an effort to facilitate the synthetic program. So, instead of cleaving the acetonide functionality associated with this compound and "reshaping" the latter into a photolysis substrate, the ester side chain was first transformed into a vinyl group thus paving the way for the introduction of a diol as required in the original synthetic plan. This procedure stands in contrast to the original route, wherein modifications to the side chain were to be made *after* the photochemical step had been carried out (see Chapter 4). It emerged that manipulations on the side chain are easier to carry out within the bicyclo[2.2.2]octene framework rather than on the photochemically-derived diquinanes. In particular, the outcome of an individual reaction was easier to interpret in the former case, as the signals in the ^{1}H NMR spectra are more widely dispersed over the spectral range and thus easier to assign. In addition, the diquinanes were often less stable than the precursor bicyclo[2.2.2]octenes which could routinely be stored at room temperature.

Scheme 3.15 shows the synthesis of photochemical product **176** from the bicyclo[2.2.2]octene precursor **156**. The latter compound was prepared according to the method described in Section 3.4.3. The reaction time for the previously mentioned reduction of substrate **156** with $NaBH_4$ in THF/MeOH was increased from 4.5 h to 16 h (to ensure the complete consumption of the starting material).

Reduction of olefin **156** gave ester **157** as a 1:1 mixture of epimers. Disappointingly, the epimerisation of undesired isomer **157b** into the desired one (**157a**) was not very efficient. Under the most favourable conditions found so far – heating with NaOMe/MeOH – a 1:2.5 mixture of esters **157a** and **157b** was

observed in the crude product An alternative was to reduce the undesired epimer **157b** with DIBAL – a rather useful reaction that gave a 1:13 mixture of epimeric aldehydes **171a** and **171b** in 70% yield – and then effect epimerisation of aldehyde **171b**. Regrettably, the epimerisation of this aldehyde was even less efficient than the equivalent process involving the corresponding ester **157b**. Thus, heating this material with DBU/benzene – the most "favourable" conditions found – gave a *ca.* 1:4.8 mixture of aldehydes **171a** and **171b**.

Scheme 3.15. *Alternative procedure for the synthesis of a photoprecursor*



Reagents and conditions: (a) $NaBH_4$, THF, MeOH, 0°C→18°C, 16 h; (b) MeONa, MeOH, 0°C→70°C, 24 h; (c) DIBAL, CH_2Cl_2, hexane, -78°C, 0.03-1.25 h; (d) DBU, benzene, 70°C, 16 h; (e) SO_3·pyridine, Et_3N, DMSO, CH_2Cl_2, 0°C, 1 h; (f) $MePPh_3Br$, NaHMDS, THF, 0°C, 4.5 h; (g) DOWEX-50, MeOH, H_2O, 110°C, 6 days; (h) *p*-TsOH·H_2O, 4-AcNH-TEMPO, CH_2Cl_2, 0°C→21°C, 17 h; (i) BzCl, Et_3N, DMAP, CH_2Cl_2, 0°C→18°C, 16 h; (j) acetophenone, acetone, hν, 15°C, 4.5 h.

After extensive purification to separate it from its epimer, ester **157a** was reduced with DIBAL and varying amounts of alcohol **170** and aldehyde **171a** were obtained. Gratifyingly, these two reduction products were easy to separate. Initial attempts to oxidise alcohol **170** with reagents such as TPAP/NMO and PDC/Celite failed. However, treatment of the latter with SO_3·pyridine gave aldehyde **171a** in reasonable yield. Methylenation of the latter was achieved by way of a Wittig reaction that proceeded uneventfully, producing olefin **172** in 60% yield. This last conversion concluded the modification of the side chain for the time being. Even though the required side-chain diol unit could have been established before the oxa-di-π-methane rearrangement, there was a risk that dihydroxylation conditions could affect the double bond within the bicyclo[2.2.2]octene moiety that is needed to induce the photoreaction. It was, therefore, decided at this point to delay the introduction of the diol functionality until after the photochemical step.

With the vinyl group in place, attention was shifted towards cleavage of the acetonide group within compound **172**. Once again, this was achieved with activated DOWEX-50 in refluxing aqueous methanol and the more accessible hydroxy group of the diol so formed was then oxidised using the oxoammonium salt **162** (Figure 3.4, page 58) derived from 4-AcNH-TEMPO. The product acyloin was then converted into the corresponding benzoate, **175**, under standard conditions. Photolysis of compound **175** using set-up (b) shown in Figure 3.5 (page 62) afforded compound **176** as a mixture of epimers in excruciatingly low yield (32%). This could be due to interference/decomposition of the terminal double bond during the photoreaction. A solution to this problem might have been the conversion of the double bond to a protected diol before the photochemistry step. However, too little material was left at this point, so this approach could not be evaluated. Instead, the small quantities of photoproduct **176** that had been obtained by the means detailed here were carried forward as described in the next Chapter.

3.5 Conclusion

This Chapter has described the elaboration of the intermolecular Diels-Alder products first encountered in Chapter 2 into substrates suitable for the proposed oxa-di-π-methane rearrangement reactions. The first sequence starting from Diels-Alder adducts **124a** and **124b** had to be abandoned, as decarbonylation of the aldehyde group caused difficulties as described in Section 3.3. However, Diels-Alder adducts **126a** and **126b** could be successfully converted into substrates for the photochemical reaction. As a result, two sets of diastomeric diquinanes **169a-d** and **176a-b** (Figure 3.6) were obtained in the oxa-di-π-methane rearrangement.

Compounds **169a**, **169b**, **176a** and **176b** possess the correct stereochemistry for the third key-step, an intramolecular alkylation reaction as detailed in the original synthetic plan, to take place. Diquinanes **169c-d** have the wrong configuration at C2 for such purposes but were taken further on the basis that epimerisation of the ester group could be effected at some point. The following Chapter details efforts to use the photochemical products **169a**, **169b**, **176a** and **176b** in the construction of the tricyclic framework of 2-isocyanoallopupukeanane.

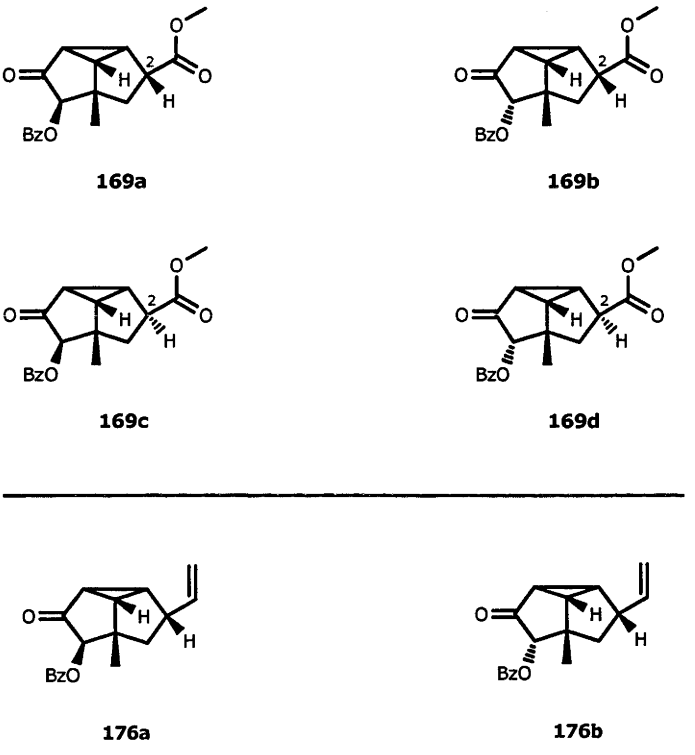


Figure 3.6. *Two sets of diquinanes available for further development*

3.6 References

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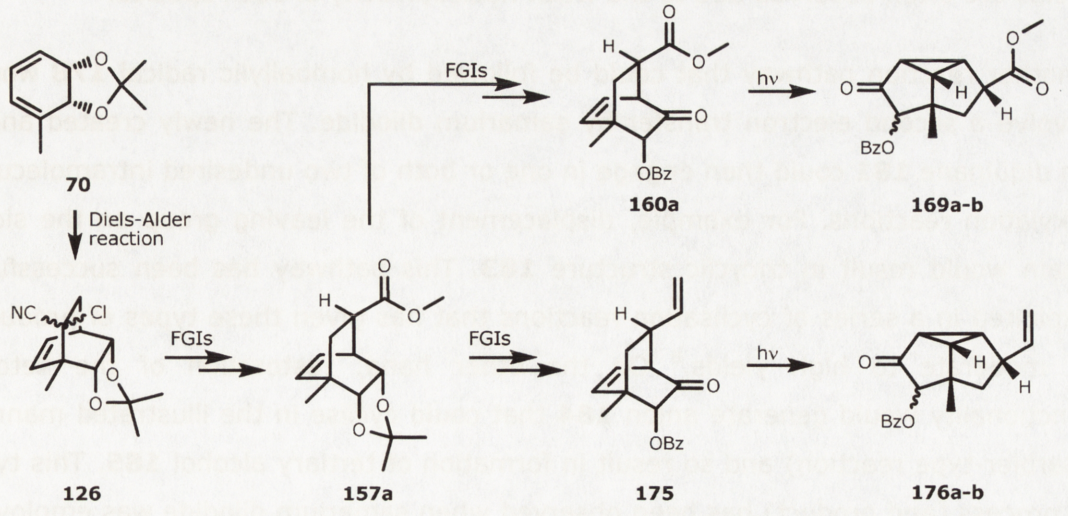
Chapter 4

Third key-step: intramolecular alkylation

4.1 Introduction

The synthetic efforts presented in the previous two Chapters reveal the challenges that were encountered in the preparation of various substrates required in the implementation of our synthetic approach to the carbocyclic framework of 2-isocyanoallopupukeanane. Ultimately, two related sequences exploiting the Diels-Alder adduct **126** and derivative **157a** allowed, as summarised in Scheme 4.1, for the preparation of two sets of photoproducts, namely compounds **169a** and **169b** as well as congeners **176a** and **176b**.

Scheme 4.1. *Summary of the reaction sequences leading to the oxa-di-π-methane rearrangement products **169a-b** and **176a-b***



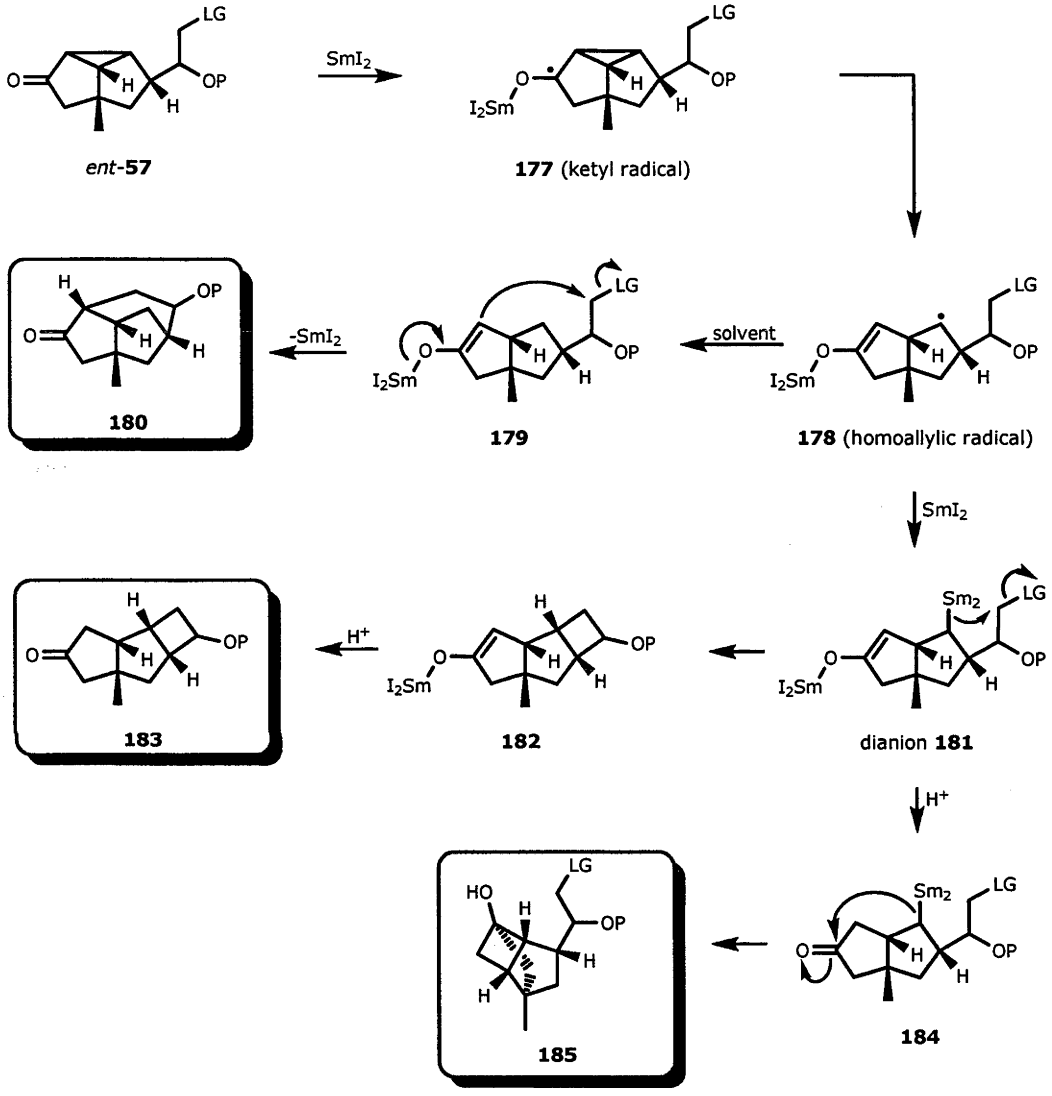
The present Chapter details work on the attempts to elaborate these photoproducts to the target natural product framework. A key feature of such studies was an investigation of the (intramolecular) reductive alkylation process enunciated in the original synthetic plan (see Scheme 1.8 on page 15). Thus, it was envisaged that this third pivotal transformation could be initiated through the reductive cleavage of the carbonyl-conjugated cyclopropane moiety associated with the diquinane structure in these systems (Scheme 4.2). Opening of the three-membered ring relieves both angular and torsional strain and is therefore a thermodynamically favoured process. The regiospecifically generated enolate that arises through this process was then expected to participate in an intramolecular alkylation process with an electrophile incorporated on the *endo*-orientated side-chain of the diquinane.

Several reagent systems are available for effecting reductive cleavage of cyclopropyl ketones.[1-4] There are, however, only very few cases where an enolate created in such a process reacts with an electrophile, and these cases involve the use of reagents such as lithium in liquid ammonia[5] and samarium diiodide.[6] The latter reagent was chosen here, due to its good reducing properties and the mildness of the reaction conditions involved. Samarium diiodide is a one-electron donor that transforms a carbonyl conjugated cyclopropyl into a ketyl radical such as **177** (Scheme 4.2). Due to the relief of strain, the latter was expected to rearrange to its ring-opened isomer **178** and "quenching" of the radical on this species through hydrogen abstraction from the solvent would give enolate **179** that should be alkylated by the pendant electrophile. This hoped-for intramolecular alkylation reaction would then deliver compound **180** that embodies the tricyclic core of the non-natural enantiomeric form of 2-isocyanoallopupukeanane. The literature details various successful efforts to trap samarium enolates of the above kind but low yields are often observed due to the weak nucleophilicity of such species.[1,6,7]

Another reaction pathway that could be followed by homoallylic radical **178** would involve a second electron transfer by samarium diiodide. The newly created anion on diquinane **181** could then engage in one or both of two undesired intramolecular alkylation reactions. For example, displacement of the leaving group on the side-chain would result in tricyclic structure **183**. This pathway has been successfully exploited in a series of cyclisation reactions that has given these types of products in moderate to high yields.[8] On the other hand, restoration of the ketone functionality would generate anion **184** that could cyclise in the illustrated manner (Barbier-type reaction) and so result in formation of tertiary alcohol **185**. This type of process (and product) has been observed when samarium diiodide was employed in the reductive ring-opening of a similar carbonyl-conjugated cyclopropane.[9]

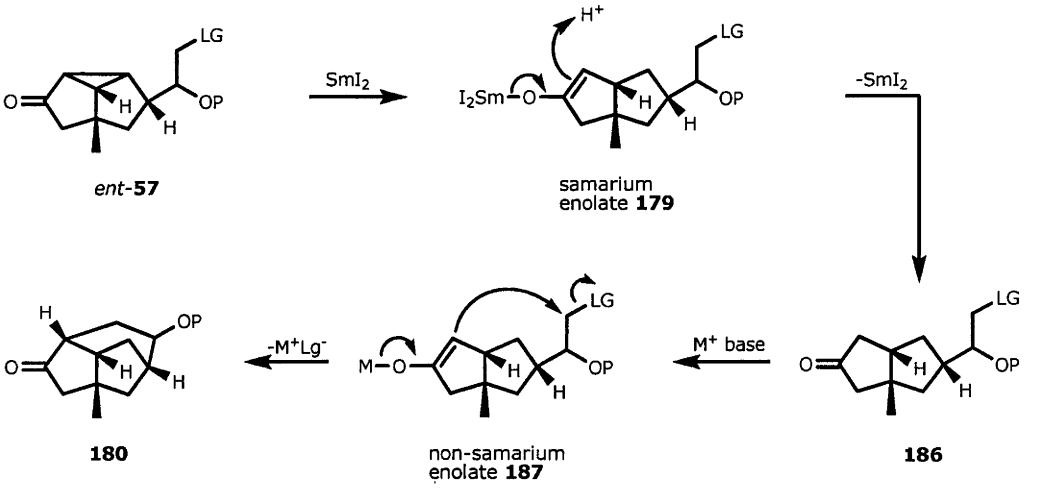
Accordingly, it was anticipated that such reaction pathways, leading to products such as **183** and **185**, could compete with the one that delivers the targeted tricycle **180**.

Scheme 4.2. *Possible outcomes of a SmI_2-induced reduction of diquinane* ent-***57***



A different approach to target **180** was also considered. Thus, conversion of intermediate **179** into ketone **186** could be followed by the formation, under conditions of kinetic control, of a 'non-samarium'-based enolate **187** (Scheme 4.3). Participation of the last species in the foreshadowed intramolecular alkylation reaction would then deliver the desired tricyclic adduct **180**.

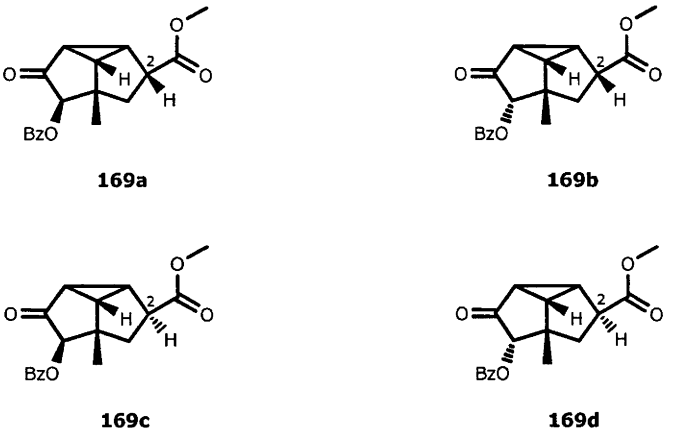
Scheme 4.3. *Alternative synthesis of alkylation product* ***180***



The research presented in this Chapter starts with a description of the modifications that were made to the structure of the photoproducts **169a**, **169b**, **176a** and **176b** in an effort to convert them into a compound of the general form *ent*-**57** (see Scheme 4.2) that could participate in the intramolecular alkylation process. The subsequent discussion focuses on the reductive cleavage/intramolecular alkylation step. It was expected that this latter process would be very demanding because conditions had to be found that suppress the formation of compounds such as **183** and **185**, and which, simultaneously, encourage the production of the desired system **180**.

4.2 The transformation of photoproducts 169a-d

As noted earlier, photoproducts **169a-d** (Figure 4.1) were obtained as epimeric mixtures. One of these was composed of epimers **169a** and **169b**, and the other consisted of compounds **169c** and **169d**. The former mixture is the one with the potential to form the non-natural enantiomer of the target compound. Due to the *endo*-orientation of the side chain, the planned intramolecular attack is possible. The latter mixture cannot be used in the same way but epimerisation at C2 within these systems would give rise to the "functional" epimers **169a** and **169b**. Unfortunately, no conditions could be found that led to the desired epimerisation at C2. Accordingly, from this point all efforts focussed on the manipulation of compounds **169a** and **169b**.



169a **169b**

169c **169d**

Figure 4.1. *The diastereomeric diquinanes* ***169a-d***

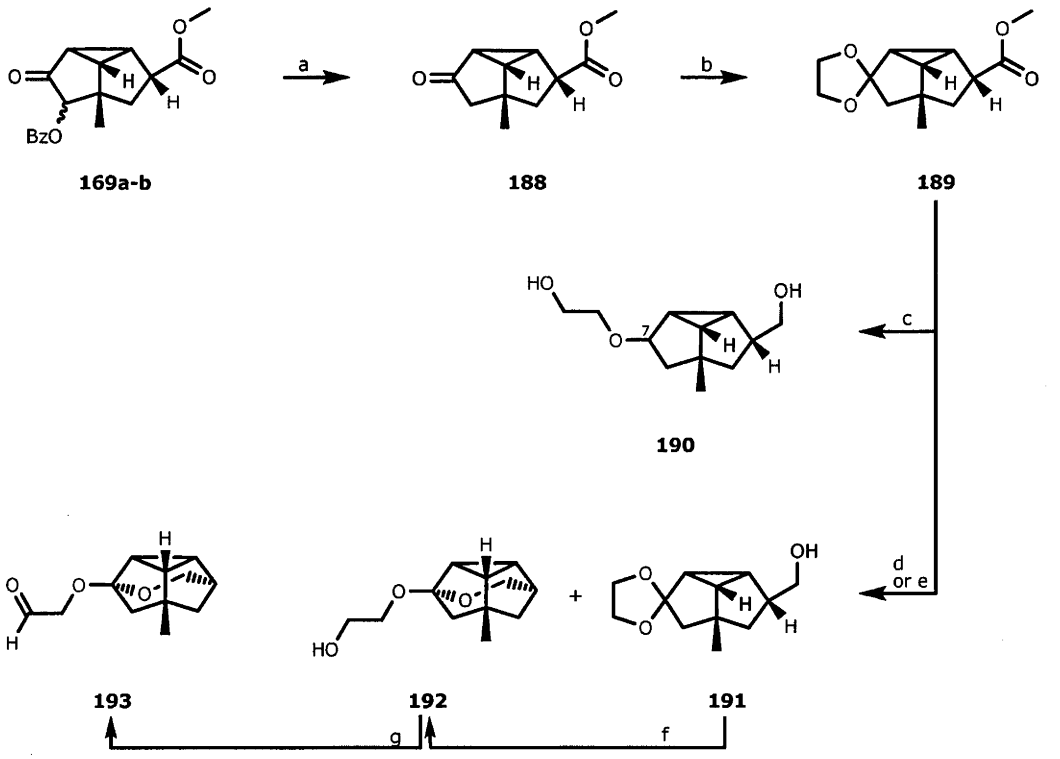
4.2.1 Chemical manipulations of '*endo*' esters 169a and 169b

Scheme 4.4 summarises the functional group manipulations that were carried out on the mixture of compounds **169a** and **169b** in an effort to prepare a system capable of engaging in the required intramolecular alkylation process. Thus, the samarium diiodide-mediated cleavage of the benzoyloxy moiety[10] within this mixture of compounds proceeded smoothly and yielded a single compound, diquinane **188**. The samarium iodide did not effect any cyclopropane ring cleavage provided that just two equivalents of the reagent were used.[9]

The next task was to convert the ester moiety into a vinyl unit, *via* methylenation of the corresponding aldehyde. However, before any such sequence could be implemented the potentially reduceable keto-group had to be protected. Accordingly, ketoester **188** was treated with ethylene glycol in the presence of *p*-TsOH and trimethyl orthoformate. In this way ketal **189** was obtained in 68% yield.

With adduct **189** in hand, the transformation of the pendant ester into a vinyl group could commence. An attempted reduction with DIBAL caused some problems at first. Thus, treatment of compound **189** with 3.5 equivalents of DIBAL not only reduced the ester moiety, but also brought about a partial cleavage of the ketal ring to give diol **190** as the single product. The structure of the latter was determined using NMR spectroscopic and mass spectrometric techniques, although the configuration at C7 was not established.

Scheme 4.4. *Manipulation of epimers **169a** and **169b***



Reagents and conditions: (a) SmI_2, THF, MeOH, -78°C, 0.1 h; (b) *p*-TsOH·H_2O, $(CH_2OH)_2$, $(CH_3O)_3CH$, benzene, 80°C, 5 h; (c) 3.5 eq DIBAL, hexane, Et_2O, -78°C→18°C, 0.7 h; (d) 1.4 eq DIBAL, toluene or CH_2Cl_2, -78°C, 2 h; (e) 1.1 eq LAH, THF, 0°C→18°C, 5.5 h; (f) H^+, H_2O, toluene or CH_2Cl_2, -78°C→18°C, 1-15 h; (g) NMO, TPAP, 4Å MS, CH_2Cl_2, 18°C, 0.5 h.

When the amount of DIBAL was reduced to 1.4 equivalents, and the reaction temperature held at -78°C varying mixtures of starting material and two unidentified alcohols were obtained. Individual experiments gave low yields and were difficult to reproduce. The mixture of product alcohols was very acid sensitive and one was converted into the other under such conditions. Oxidation of the acid-generated alcohol with NMO/TPAP gave an aldehyde that was eventually identified as compound **193**. On this basis, the substrate alcohol was assumed to be **192** and this is formed through an acid-catalysed transacetalisation process from isomer **191**, the direct reduction product of ester **189**. It should be noted that reduction of ester **189** with LAH in THF furnished, after work-up under basic conditions, only alcohol **191** and that exposure of the latter to a saturated aqueous potassium sodium tartrate solution did not cause transacetalisation. Given the complexities of the situation just described further manipulation of compounds derived from photoproducts **169a-b** was abandoned. Rather, attention was redirected towards the modification of photoproducts **176a** and **176b** as described in the following Section.

4.3 Elaboration of photoproducts 176a and 176b

The mixture of diquinanes **176a** and **176b** was treated with samarium diiodide so as to remove the benzoyloxy group in the same way as described above (Scheme 4.5). The next task consisted of the conversion of the terminal double bond on the product olefin **194** (obtained in 54%) into a vicinal diol. In the hope of obtaining a single diastereoisomer, the requisite dihydroxylation reaction was carried out under Sharpless conditions.* Disappointingly, treatment of diquinane **194** with AD-mix-α only resulted in a 1:1:1 mixture of starting material and the epimeric forms of diol **195**. AD-Mix-β gave no reaction at all. The use of other AD ligands, notably the pyrimidine-linked ligand $(DHQ)_2PYR$,[11] could have changed the stereoselectivity of the reaction but no experimentation concerning this matter was carried out in order to save the small amounts of substrate remaining at this point. Instead, diquinane **194** was simply treated with osmium tetroxide and NMO and a 1:1 mixture of the epimeric forms of compound **195** (48%) was thus obtained. The two isomers were inseparable and, therefore, subjected to the next step of the reaction sequence as a mixture.

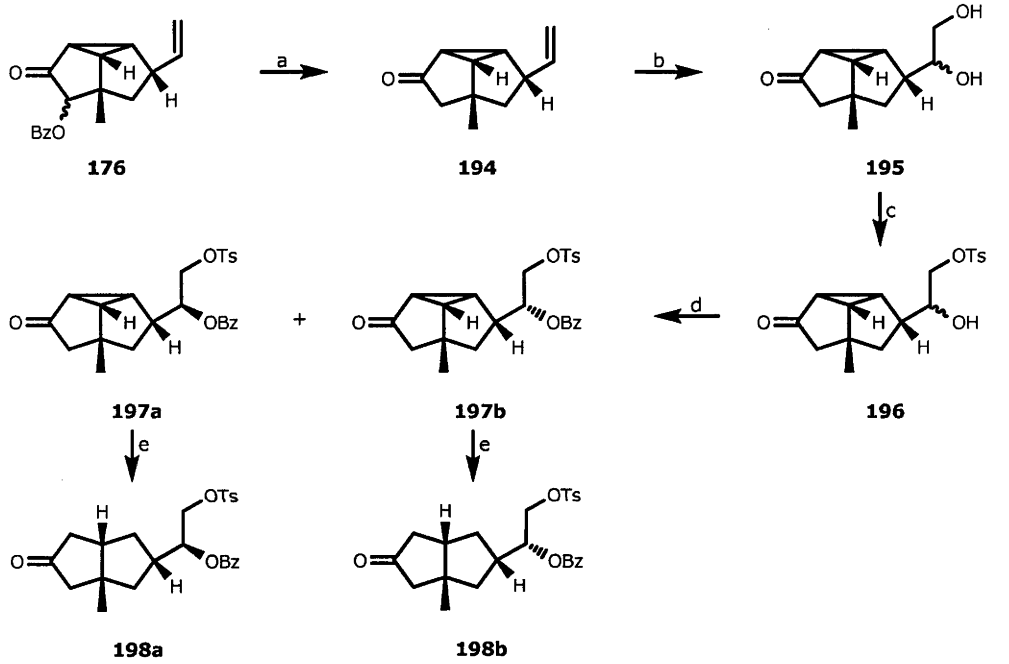
The time had now come to prepare the molecule for the intramolecular alkylation step by installation of a suitable leaving group on the primary hydroxy group. Monotosylation of the diol with *p*-TsCl and using dibutyltin oxide[12] as catalyst provided the epimeric monotosylates **196** in 77% combined yield. Once again, the two products were inseparable so the mixture was subjected to the next step of the reaction sequence, namely *O*-benzoylation. In the event, introduction of a benzoyloxy group onto the remaining free alcohol of tosylate **196**, which could be accomplished under standard conditions, provided a chromatographically separable mixture of the esters **197a** and **197b**. These compounds, which were carried forward individually, were fully characterised through 1- and 2-D NMR spectroscopic and mass spectrometric analyses. The configurations at the stereocentres carrying the benzoyloxy group in compounds **197a** and **197b** could not be determined at this point but were subsequently established through X-ray analysis of a derivative (*vide infra*).

At last the time had come for the testing of the pivotal intramolecular alkylation reaction and tosylate **197a** was used as the substrate for this purpose. Treatment of this compound with samarium diiodide in methanol and THF did not effect any change at -78°C but when the reaction mixture was warmed to 0°C a new compound was observed by thin layer chromatography. At ambient temperatures

* It needs to be pointed out that the obtension of a mixture of epimers would not pose any concerns, as the secondary alcohol group will be oxidized to a ketone at a later stage. It would however be advantageous to work with only one isomeric series, to facilitate the interpretation of ^1H NMR spectra.

the starting material was consumed at a good rate but the cyclopropane ring-cleaved compound **198a** was the only isolable product of the reaction. This type of outcome is in accord with earlier observations[9,13] since organosamarium species and samarium enolates tend to be readily quenched under protic conditions and in which case the intramolecular alkylation reaction would not take place. The outcome might have been different if an aprotic solvent such as DMPU had been used.[1,6] However, far too little material was available to allow for a testing of this possibility.

Scheme 4.5. *Modification of diquinane **176***



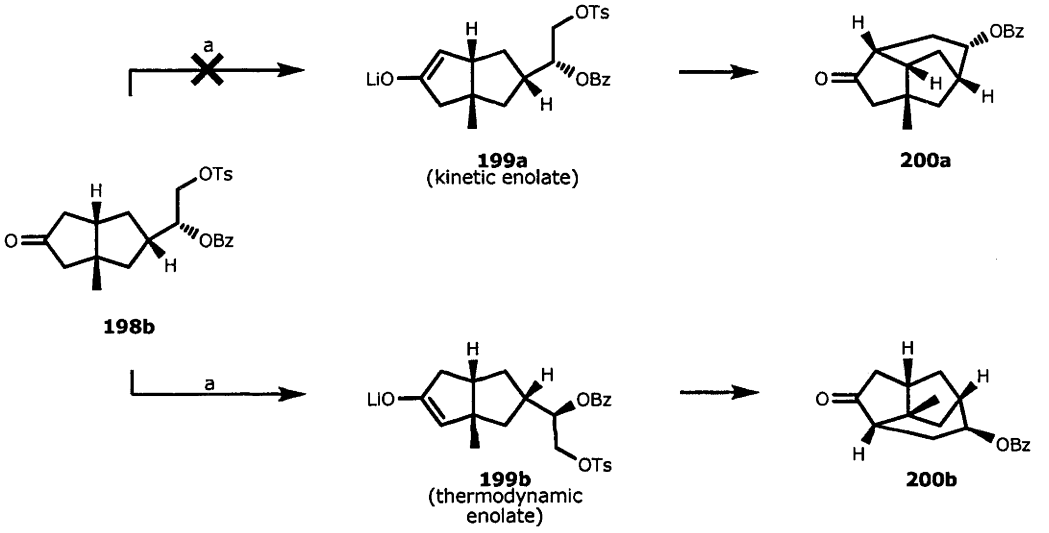
Reagents and conditions: (a) SmI_2, MeOH, THF, -78°C, 0.1 h; (b) OsO_4, NMO, ^tBuOH, H_2O, acetone, 0°C→18°C, 4.5 h; (c) Et_3N, Bu_2SnO, TsCl, CH_2Cl_2, 18°C, 5.5 h; (d) BzCl, Et_3N, DMAP, CH_2Cl_2, 0°C→18°C, 14 h; (e) SmI_2, MeOH, THF, -78°C→0°C→18°C, 6-8 h.

Since the amount of diquinane **198a** that was obtained was too small to carry further, the explorations of the hoped-for reductive alkylation reaction were continued using epimer **197b**. Upon exposure of this material to samarium diiodide at 18°C the ring-opened product **198b** was obtained as the major product of the reaction. Intramolecular alkylation was then induced through treatment of the purified species **198b** with base. It was expected that under the conditions used the kinetic enolate **199a** (Scheme 4.6) would be generated and that intramolecular alkylation of this species would then deliver adduct **200a** embodying the carbon skeleton of the non-natural enantiomer of 2-isocyanoallopupukeanane.

When adduct **198b** was treated dropwise with LiHMDS in THF followed by stirring at ambient temperature for six hours, a new compound was observed. Purification and

spectral analysis of the product showed that the reaction had caused a loss of the elements of *p*-TsOH. The structure of the product was confirmed through a single-crystal X-ray analysis (Figure 4.2) and thus revealing that it was compound **200b**. This confirmed that the intramolecular alkylation had indeed taken place but in an unexpected way. Structure **200b** has the carbon skeleton of the natural enantiomer of the target compound but with the angular methyl group in the wrong position. The conversion **198b** to **200b** presumably involves an intramolecular alkylation reaction of the thermodynamically more stable enolate **199b**. The stability of the latter derives from a greater reduction in torsional strain (between the angular

Scheme 4.6. *Intramolecular alkylation within adduct **198b***



Reagents and conditions: (a) LiHMDS, THF, 18°C, 6 h.

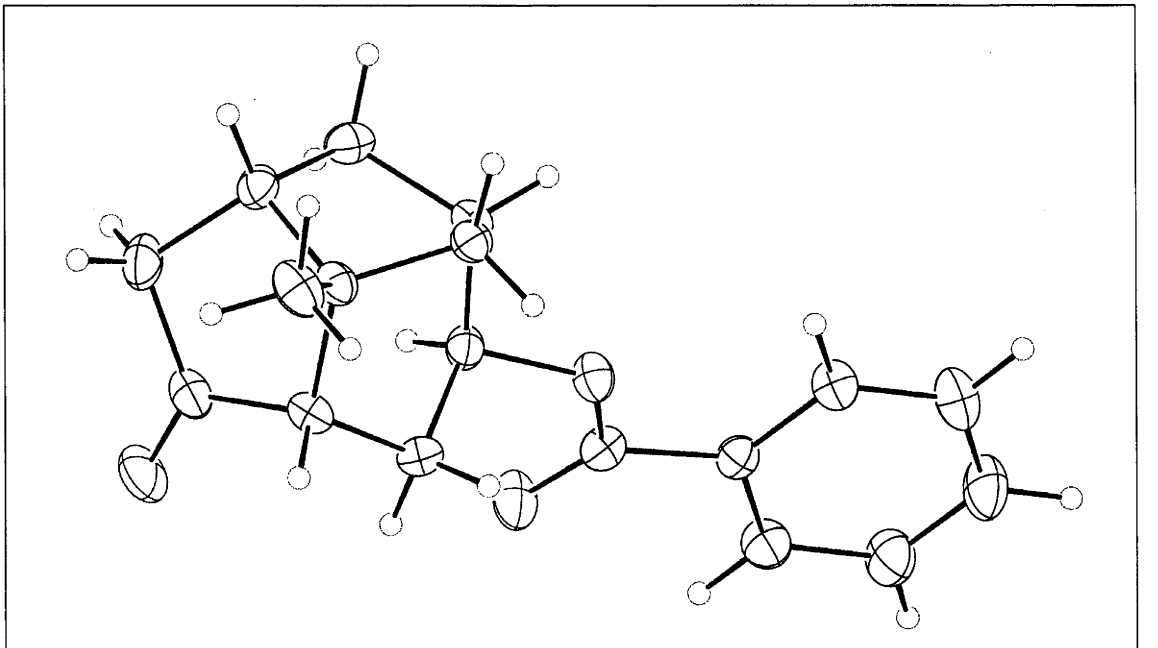


Figure 4.2. *ORTEP derived from the single-crystal X-ray analysis of compound **200b***

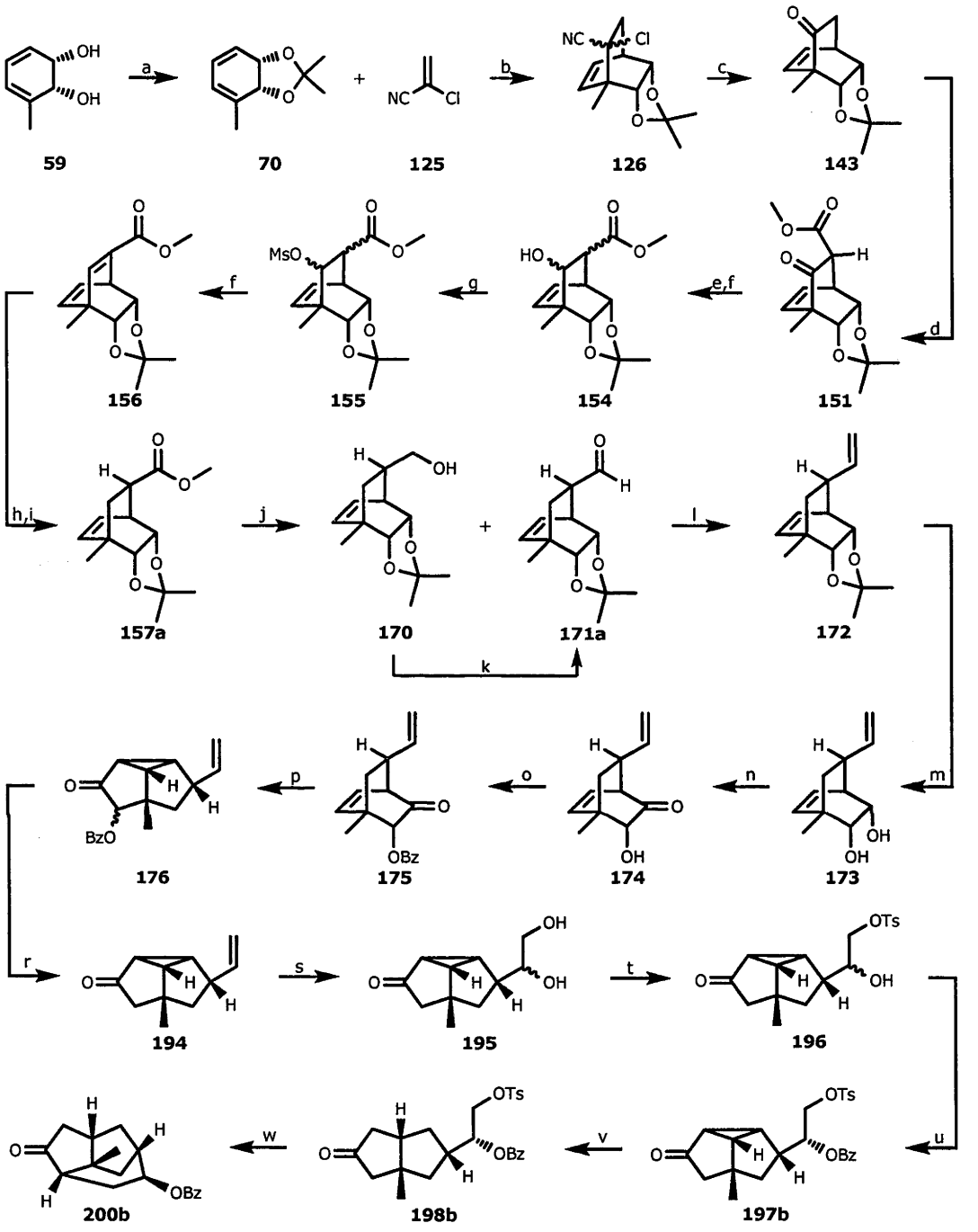
methyl group and the *syn*-1,2-related methylene proton adjacent to the carbonyl group). This release of strain is greater than would be encountered in the equivalent process leading to **199a** (where the corresponding reduction in torsional strain would "only" be that arising from loss of the interaction between the angular hydrogen and the *syn*-1,2-related methylene proton adjacent to the carbonyl group).

In conclusion, the work described in this thesis has demonstrated that efforts directed towards the total synthesis of the non-natural enantiomeric form of 2-isocyanoallopupukeanane resulted in the construction of the carbocyclic skeleton of the natural enantiomer of the target compound albeit with the angular methyl group in the wrong position. It is envisaged that the pivotal intramolecular alkylation reaction used in this work could generate the carbon skeleton of the non-natural enantiomer of the natural product if conditions could be found that would allow for the generation of the kinetic enolate **199a**. Work directed towards such ends is now underway in the Banwell laboratories. Section 4.4 provides an overview of the reactions that contributed to the assembly of ketone **200b**, while Section 4.5 closes off this Chapter with a discussion about future work to be carried out.

4.4 Summary of the successful reaction sequence

Scheme 4.7 shown directly below summarises the reaction sequence that has lead to the formation of compound **200b** incorporating the tricyclic framework of 2-isocyanoallopupukeanane.

Scheme 4.7. *Summary of the sequence leading to final product **200b***



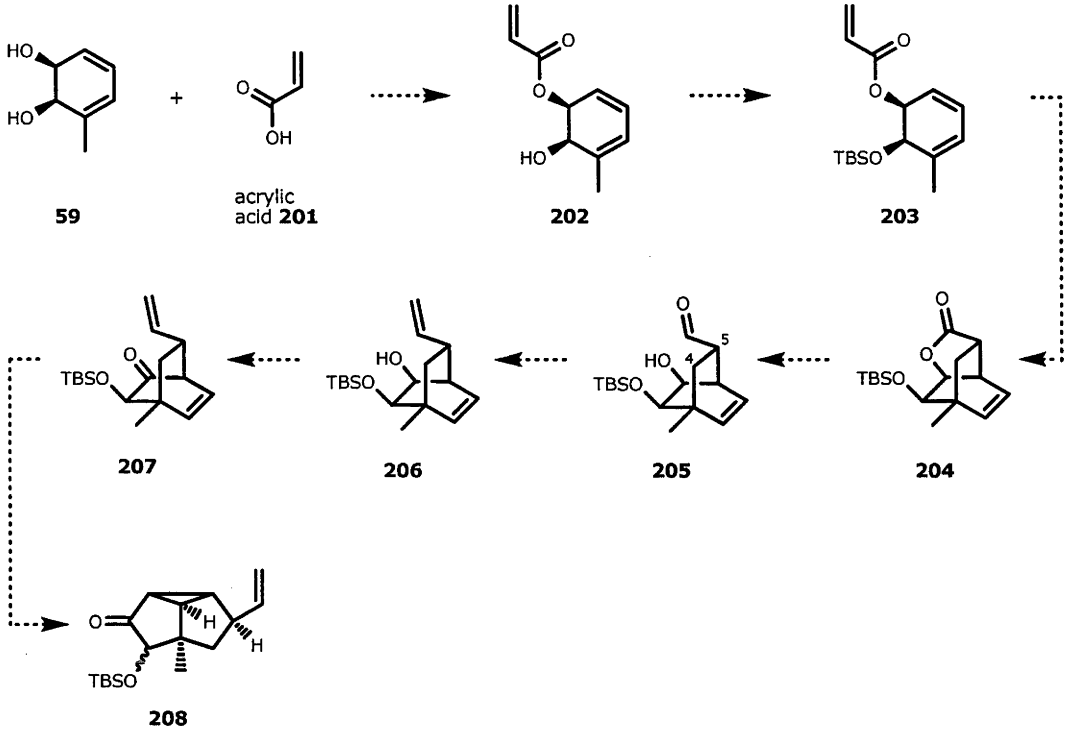
Reagents and conditions: (a) *p*-TsOH·H_2O, DMP, 0°C, 2 h; (b) toluene, 92°C, 24 h; (c) $Na_2S·9H_2O$, EtOH, 92°C, 15 h; (d) i. LiHMDS, Et_2O, THF, -78°C, 3.3 h; ii. NCCOOMe, -78°C, 5.7 h; (e) $NaBH_4$, EtOH, 0°C→18°C, 1.5 h; (f) DBU, benzene, 70-72°C, 15-21 h; (g) MsCl, Et_3N, CH_2Cl_2, 0°C→18°C, 5 h; (h) $NaBH_4$, THF, MeOH, 0°C→18°C, 16 h; (i) MeONa, MeOH, 0°C→70°C, 24 h; (j) DIBAL, CH_2Cl_2, hexane, -78°C, 1.25 h; (k) SO_3·pyridine, Et_3N, DMSO, CH_2Cl_2, 0°C, 1 h; (l) $MePPh_3Br$, NaHMDS, THF, 0°C, 4.5 h; (m) DOWEX-50, MeOH, H_2O, 110°C, 6 days; (n) *p*-TsOH·H_2O, 4-AcNH-TEMPO, CH_2Cl_2, 0°C→21°C, 17 h; (o) BzCl, Et_3N, DMAP, CH_2Cl_2, 0°C→18°C, 16 h; (p) acetophenone, acetone, hv, 15°C, 4.5 h; (r) SmI_2, MeOH, THF, -78°C, 0.1 h; (s) OsO_4, NMO, ^tBuOH, H_2O, acetone, 0°C→18°C, 4.5 h; (t) Et_3N, Bu_2SnO, TsCl, CH_2Cl_2, 18°C, 5.5 h; (u) (i) BzCl, Et_3N, DMAP, CH_2Cl_2, 0°C→18°C, 14 h; (ii) separation of isomers; (v) SmI_2, MeOH, THF, -78°C→0°C→18°C, 6-8 h; (w) LiHMDS, THF, 18°C, 6 h.

4.5 Future plans

Section 4.3 showed how an intramolecular alkylation reaction resulted in the construction of the carbocyclic skeleton of the natural enantiomer of 2-isocyano-allopupukeanane albeit with the methyl group in the wrong place. The reaction presumably proceeded *via* the formation of a thermodynamic enolate instead of the anticipated kinetic one, and this is believed to be due to the addition of base to substrate **198b**. On the other hand, the slow addition of substrate **198b** to an excess amount of base is expected to prevent equilibration to a thermodynamic enolate due to the trapping of the kinetic enolate in the non-reversible intramolecular alkylation. At this point, the amount of material available to work with was insufficient to allow these ideas to be pursued, but plans to continue on this route are now underway.

Building on the work described in this thesis, a revised strategy has been proposed in an effort to decrease the number of synthetic steps required to prepare the photoproduct **176**. The revised route involves the preparation of an ester as a substrate for an intramolecular Diels-Alder reaction. A difference between this and the earlier strategies is that esterification would now occur at the hydroxyl group on toluenediol **59** that is remote from the methyl group (Scheme 4.8). Thus, esterification of toluenediol **59** with acrylic acid **201** would be expected to give ester **202**. After protection of the remaining free hydroxy group, this ester would be subjected to an IMDA reaction. Such a reaction has already been performed with a similar substrate.[14] The product **204** so obtained would have several convenient features. In particular, the exclusive formation of an *exo*-adduct would be expected due to the short linker chain connecting the diene and dienophile. The latter could, in turn, be exploited for the formation of the pendant chain. Reductive cleavage of the lactone ring would give adduct **205**, with the desired stereocentre on C5. Furthermore, C4 would now be "substituent-free", thereby significantly reducing the number of reaction steps that had to be carried out previously to remove the electron-withdrawing group. Adduct **205** could be further modified into the substrate for photolysis, **207**, by following steps described earlier in this thesis. This substrate could either be subjected to the oxa-di-π-methane rearrangement as is or, to prevent the vinyl side chain from interfering with the photochemical reaction, after further modification (dihydroxylation) of the side-chain. Elaboration of diquinane **208** to the precursor for the intramolecular alkylation reaction, **198b**, would then exploit the protocols described earlier in this Chapter.

Scheme 4.8. *Revised plan for the preparation of photoproduct **208***



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Chapter 5

Experimental procedures

5.1 General procedures

Proton (^{1}H) and carbon (^{13}C) nuclear magnetic resonance (NMR) spectra were recorded on a Varian Mercury 300 (^{1}H at 300 MHz, ^{13}C at 75 MHz), Varian Inova 500 (^{1}H at 500 MHz, ^{13}C at 125 MHz) or Varian Inova 600 (^{1}H at 600 MHz, ^{13}C at 150 MHz) spectrometer. Signals arising from the residual protio-forms of the solvent were used as the internal standards. Chemical shifts are recorded as δ values in parts per million (ppm). The residual $CHCl_3$ peak (δ 7.26), the residual benzene peak (δ 7.15) and the central residual acetone pentet peak (δ 2.05) were used as references. ^{1}H NMR data are recorded as follows: chemical shift (δ) (multiplicity, coupling constant(s) *J* (Hz), relative integral) where multiplicity is defined as: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet or combinations of the above. The central peak of the $CDCl_3$ "triplet" (δ 77.0), the central peak of the benzene-d_6 "triplet" (δ 128.0) and the central peak of the acetone-d_6 "septet" (δ 30.60) were used as references for proton-decoupled ^{13}C NMR spectra. The data are given as: chemical shift (δ) (protonicity), where protonicity is defined as: C=quaternary; CH=methine; CH_2=methylene; CH_3=methyl. The assignment of signals observed in various NMR spectra were often assisted by conducting an attached proton test (APT), gradient homonuclear ($^{1}H/^{1}H$) correlation spectroscopy (gCOSY), gradient heteronuclear ($^{1}H/^{13}C$) correlation spectroscopy (gHSQC and gHMBC) or nuclear Overhauser effect (NOE) experiments.

Infrared (IR) spectra were measured on a Perkin-Elmer 1800 Series or Spectrum One FT-IR Spectrometer. A sample of the compound to be analysed was dissolved

in $CDCl_3$. In some cases a different solvent was used and this is indicated in brackets. A drop of the resulting solution was placed on a KBr disk and the solvent evaporated.

A VG Fisons AutoSpec three sector (E/B/E) double focussing mass spectrometer was used to obtain low and high-resolution electron impact (EI) mass spectra. Low and high-resolution electrospray impact (ESI) mass spectra were obtained on a VG Quattro II triple quadrupole MS instrument operating in either positive or negative ionisation modes. Gas chromatography mass spectra (GC-MS) were obtained on an Agilent 5973N instrument. Low resolution mass spectral data are recorded as follows: m/z value (relative intensity as a percentage of the base peak).

Optical rotations were measured with a Perkin-Elmer 241 or 343 polarimeter at the sodium-D line (589 nm), and at the concentrations (*c*) (g/100 ml) and temperatures (T, °C) indicated. The measurements were carried out in a cell with a path length (l) 1 dm, using spectroscopic grade $CHCl_3$ as solvent. Specific rotations $[\alpha]_D^T$ were calculated using the equation $[\alpha]_D^T = (100 \cdot \alpha)/(c \cdot l)$ and are given in 10^{-1} deg cm^2 g^{-1}.

Melting points (m.p.) were measured on a Reichert hot-stage microscope apparatus or a Stanford Research Systems Optimelt-Automated Melting Point System and are uncorrected.

Elemental analyses were performed by the Australian National University's Microanalytical Unit at the Research School of Chemistry, in Canberra.

High-pressure promoted reactions were carried out using a PSIKA Pressure Systems Ltd. 20 kbar Pressure Reaction System apparatus. A solution of the starting materials in dichloromethane was subjected to pressure contained in a Teflon® compressible reaction vessel.

Photochemical reactions were performed using a Philips 125 W HPL-N Hg arc lamp or an Ace Glass 450 W immersion lamp housed in a quartz water-cooled jacket.

Analytical thin layer chromatography (TLC) was performed on glass backed silica gel 60 F_{254} plates as supplied by Merck. Eluted plates were visualised using a 254 nm UV lamp and/or by treatment with a phosphomolybdic acid dip made up of 37.5 g phosphomolybdic acid, 7.5 g ceric sulfate, 37.5 g conc. sulphuric acid and 720 ml water, followed by heating. Flash chromatography was conducted using the analytical grade solvents indicated and silica gel 60 (40-63 μm) as supplied by Carlo Erba Reagents.

High-pressure liquid chromatography (HPLC) was carried out using a system that consists of a Waters 600 E quaternary solvent delivery system with inline degasser, a Rheodyne 7725i ejection valve (5-20 µl loops) and a Waters 2996 Photodiode Array Detector device. Peaks were detected using a UV lamp or a 2414 differential refractive index detector.

Starting materials and reagents were generally available from the Sigma-Aldrich, Merck, Alfa Aesar or Acros Chemical Companies and were used as supplied. Occasionally some liquids were distilled and solids recrystallised prior to use. *Cis*-1,2-dihydrocatechol **59** was provided by Questor, Queens University of Belfast, Northern Ireland (http://questor.qub.ac.uk/newsite/contact.htm). Similarly, 4-AcNH-TEMPO was supplied Professor T. Bobbitt, University of Connecticut, USA. The latter two reagents were used as supplied.

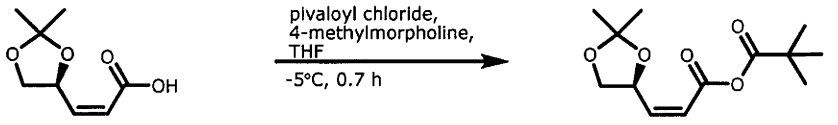
Drying agents and other inorganic salts were purchased from the AJAX, BDH or Unilab Chemical Companies. Solvents were either distilled in a still or obtained from a Glass Contour solvent purification system that is based upon a technology originally described by Grubbs *et al.*[1] Spectroscopic grade solvents were used for all analyses.

In the cases were distilled solvents were used, THF and diethyl ether were distilled from sodium benzophenone ketyl. Methanol was distilled from its magnesium alkoxide salts. Benzene and toluene were distilled from sodium wire. Dichloromethane was distilled from calcium hydride.

Glassware was soaked and washed in a solution of Pyroneg® and water before being rinsed with water then acetone and oven-dried at 120°C. All moisture-sensitive reactions were conducted in a system that was evacuated and flushed three times with dry nitrogen or argon prior to use. Manipulations under protective gas occurred using standard Schlenk techniques. Reaction temperatures above 18°C refer to the external oil bath temperatures.

5.2 Experimental procedures associated with work described in Chapter 2

(*S,Z*)-3-(2,2-Dimethyl-1,3-dioxolan-4-yl)acrylic pivalic anhydride (87)

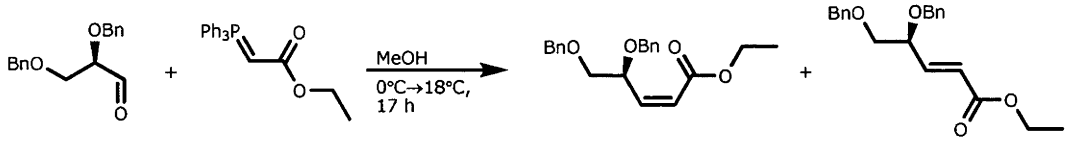


80 **87**

A solution of carboxylic acid **80** (100 mg, 581 μmol) in THF (4.20 ml) was cooled to -5°C then freshly distilled 4-methylmorpholine (0.14 ml, 1.28 mmol, 2.2 eq) was added dropwise and the resulting mixture stirred at -5°C for 0.17 h. Pivaloyl chloride (86 μl, 697 μmol, 1.2 eq) was then added and after 0.5 h the reaction mixture was warmed to 18°C then loaded directly onto the top of a flash chromatography column loaded with neutral alumina. This was eluted with 1:39 v/v ethyl acetate/hexane and after concentration of the relevant fractions a *ca.* 1:2.5 mixture of an unknown compound and the mixed anhydride **87** (99 mg) was obtained as a clear, colourless oil.

Mixed anhydride **87**; R_f = 0.6 in 1:39 v/v ethyl acetate/hexane (alumina)
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.60 (dd, J = 11.5 and 6.6 Hz, 1H), 5.87 (dd, J = 11.5 and 1.8 Hz, 1H), 5.50-5.42 (complex m, 1H), 4.42 (dd, J = 8.4 and 7.0 Hz, 1H), 3.65 (dd, J = 8.4 and 6.6 Hz, 1H), 1.45 (s, 3H), 1.38 (s, 3H), 1.25 (s, 9H);
^{13}C NMR (75 MHz, $CDCl_3$): δ 173.7, 161.2, 154.6, 119.1, 110.0, 73.6, 69.1, 39.9, 26.5, 26.4 (3 carbons), 25.2;
MS (EI, 70 eV) m/z: 256 ($M^{+\bullet}$, 2%), 241 [$(M\text{-}CH_3\bullet)^+$, 6], 155 (72), 97 (85), 85 (78), 69 (76), 57 (83), 43 (100).

Ethyl (*S,Z*)-4,5-bis(phenylmethoxy)pent-2-enoate (91a) and Ethyl (*S,E*)-4,5-bis(phenylmethoxy)pent-2-enoate (91b).



90 **82** **91a** **91b**

A solution of aldehyde **90**[2] (1.21 g, 4.47 mmol) in methanol (20 ml) was cooled to 0°C then treated with ylide **82**[3] (2 g, 5.74 mmol, 1.3 eq). The resulting mixture was stirred at 0°C→18°C for 17 h then the solvent was removed under reduced pressure to give a damp, light-yellow solid comprised of a 4.5:1 mixture of esters **91a** and **91b** as determined by ^{1}H NMR analysis. The solid was subjected to column chromatography (silica, 1:9 v/v ethyl acetate/hexane) to afford two fractions, A and B.

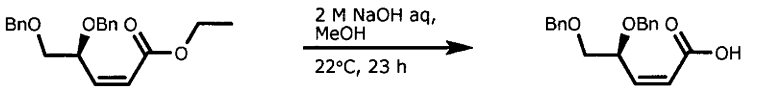
Concentration of fraction A (R_f = 0.3 in 1:9 v/v ethyl acetate/hexane) afforded ester **91a** (924 mg, 61%) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40-7.26 (complex m, 10H), 6.30 (ddd, J = 11.8, 8.2 and 0.7 Hz, 1H), 5.96 (ddd, J = 11.8, 1.4 and 0.7 Hz, 1H), 5.38-5.30 (complex m, 1H), 4.68-4.54 (complex m, 4H), 4.17 (dq, J = 7.1 and 0.5 Hz, 2H), 3.74-3.64 (complex m, 2H), 1.28 (dt, J = 7.1 and 0.5 Hz, 3H);
^{13}C NMR (75 MHz, $CDCl_3$): δ 165.6 (C), 147.8 (CH), 138.3 (C), 138.2 (C), 128.2 (CH), 128.2 (CH), 127.7 (CH), 127.5 (CH), 127.4 (CH), 122.3 (CH), 74.6 (CH), 73.0 (CH_2), 72.2 (CH_2), 71.5 (CH_2), 60.3 (CH_2), 14.1 (CH_3);
IR ν_{max} (KBr) 3031, 2981, 2927, 2903, 2860, 1717, 1496, 1454, 1412, 1386, 1364, 1299, 1219, 1192, 1095, 1075, 1028, 826, 735, 697 cm^{-1};
MS (ESI, +ve ion mode) *m/z*: 363 [$(M+Na)^+$, 100%], 341 [$(M+H)^+$, 7], 181 (63), 115 (29), 91 (48);
HRESMS Found: $(M+Na)^+$, 363.1563. Calculated for $C_{21}H_{24}O_4$ $(M+Na)^+$, 363.1572.

Concentration of fraction B (R_f = 0.3 in 1:9 v/v ethyl acetate/hexane) afforded a *ca.* 1:1.4 mixture of esters **91a** and **91b** (243 mg, 16%) as a clear, colourless oil. ^{1}H NMR signals due to compound **91b** are recorded below.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40-7.26 (complex m, 10H), 6.91 (dd, J = 15.8 and 5.8 Hz, 1H), 6.13 (dd, J = 15.8 and 1.4 Hz, 1H), 4.69-4.50 (complex m, 4H), 4.27-4.20 (complex m, 1H, partially obscured), 4.22 (q, J = 7.1 Hz, 2H), 3.65-3.54 (complex m, 2H), 1.31 (t, J = 7.1 Hz, 3H);

(*S,Z*)-4,5-*bis*(Benzyloxy)pent-2-enoic acid (89).

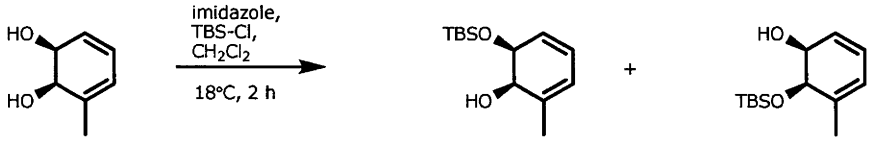


91a **89**

Sodium hydroxide (2.4 ml of a 2 M aq. solution) was added to a solution of ester **91a** (804 mg, 2.36 mmol) in methanol (13.2 ml) and the resulting mixture was stirred at 22°C. After 23 h the starting material had been consumed, so the pH of the mixture was adjusted to approximately 4-5 using hydrochloric acid (1 M aq. solution). The resulting mixture was extracted with dichloromethane (3 x 15 ml) and the combined organic extracts were washed with brine (1 x 15 ml) then dried (magnesium sulfate), filtered and concentrated under reduced pressure. The resulting light yellow oil (726 mg) was subjected to column chromatography (silica, 1:1 v/v ethyl acetate/hexane) and concentration of the appropriate fractions then gave acid **89** (678 mg, 92%) as a clear, colourless oil.

R_f = 0.3 in 1:2 v/v ethyl acetate/hexane;
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37-7.24 (complex m, 10H), 6.40 (dd, J = 11.9 and 8.4 Hz, 1H), 5.98 (dd, J = 11.9 and 1.2 Hz, 1H), 5.28-5.21 (complex m, 1H), 4.65-4.53 (complex m, 4H), 3.73-3.62 (complex m, 2H), signal due to carboxylic acid proton not observed;
^{13}C NMR (75 MHz, $CDCl_3$): δ 170.5 (C), 150.2 (CH), 138.0 (C), 128.3 (CH), 127.8 (CH), 127.7 (CH), 127.6 (CH), 121.7 (CH), 74.8 (CH), 73.3 (CH_2), 72.0 (CH_2), 71.8 (CH_2);
IR ν_{max} (KBr) 3086, 3063, 3031, 2863, 1718, 1697, 1645, 1496, 1453, 1434, 1391, 1365, 1296, 1250, 1192, 1096, 1073, 1027, 929, 908, 829, 735, 697 cm^{-1};
MS (ESI, -ve ion mode) *m/z*: 311 [$(M-H)^-$, 54%], 203 (100);
HRESMS Found: $(M-H)^-$, 311.1277. Calculated for $C_{19}H_{20}O_4$ $(M-H)^-$, 311.1283.
Optical rotation $[\alpha]_D^{18}$ +18.4 (*c* 1, $CHCl_3$).

(1*R*,6*S*)-6-(*tert*-Butyldimethylsilyloxy)-2-methylcyclohexa-2,4-dien-1-ol (74a) and (1*S*,6*R*)-6-(*tert*-Butyldimethylsilyloxy)-5-methylcyclohexa-2,4-dien-1-ol (74b).



59 **74a** **74b**

A solution of diol **59** (1 g, 7.93 mmol) in dichloromethane (7 ml) was treated with imidazole (1.46 g, 21.41 mmol, 2.7 eq) then a solution of TBS-Cl (1.31 g, 8.72 mmol, 1.1 eq) in dichloromethane (2 ml) was added dropwise over 0.17 h. The ensuing mixture was stirred at 18°C and, after 2 h, quenched with sodium chloride (15 ml of a 1.5 M aq. solution). The separated aqueous phase was extracted with diethyl ether (3 x 15 ml) then the combined organic phases were washed with brine (1 x 15 ml) before being dried (magnesium sulfate), filtered and concentrated under reduced pressure. The orange oil so obtained was comprised of a 2.2:1 mixture of monoprotected diols **74a** and **74b** as determined by ^{1}H NMR spectroscopic analysis. This material was subjected to column chromatography (silica, 1:19 v/v ethyl acetate/hexane) and thus affording two fractions, A and B.

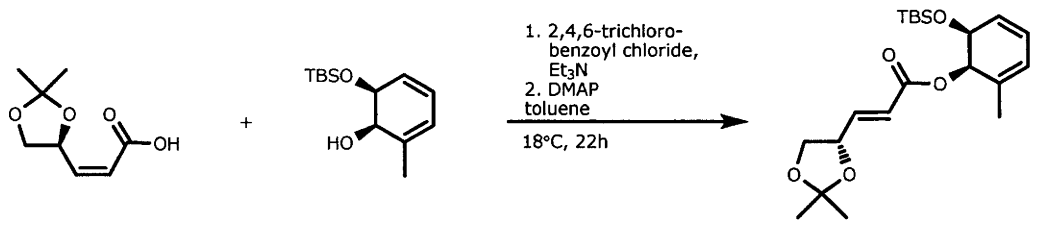
Concentration of fraction A (R_f = 0.3 in 1:19 v/v ethyl acetate/hexane) afforded compound **74a** (1.12 g, 59%) as a clear, colourless oil.

^{1}H NMR [500 MHz, $(CD_3)_2CO$)]: δ 5.89-5.86 (complex m, 1H), 5.72-5.69 (complex m, 2H), 4.42-4.41 (complex m, 1H), 3.95-3.93 (complex m, 1H), 3.22 (d, *J* = 6.3, 1H), 1.90 (complex m, 3H), 0.95 (s, 9H), 0.16 (d, *J* = 2.4 Hz, 6H);
^{13}C NMR [125 MHz, $(CD_3)_2CO$]: δ 140.3 (C), 129.0 (CH), 125.9 (CH), 120.7 (CH), 72.5 (CH), 72.4 (CH), 71.8 (CH), 71.8 (CH), 27.0 (CH_3), 21.2 (CH_3), 19.6 (C), -3.6 (CH_3), −3.8 (CH_3);
IR ν_{max} (KBr) 3558, 2954, 2930, 2883, 2857, 1472, 1462, 1396, 1253, 1161, 1093, 1045, 1037, 1004, 949, 940, 906, 879, 856, 836, 811, 777, 744, 679 cm^{-1};
MS (ESI, +ve ion mode) *m/z*: 263 [$(M+Na)^+$, 100%], 102 (18);
HRESMS Found: $(M+Na)^+$, 263.1434. Calculated for $C_{13}H_{24}O_2Si$ $(M+Na)^+$, 263.1443.
Optical rotation $[\alpha]_D^{16}$: +74.6 (*c* 0.95, $CHCl_3$).

Concentration of fraction B (R_f = 0.2 in 1:19 v/v ethyl acetate/hexane) gave compound **74b** (215 mg, 11%) as a clear, colourless oil.

^{1}H NMR [500 MHz, $(CD_3)_2CO$)]: δ 5.90 (dd, J = 9.5 and 5.1 Hz, 1H), 5.81 (dd, J = 9.5 and 4.2 Hz, 1H), 5.72-5.70 (complex m, 1H), 4.26-4.24 (complex m, 1H), 4.09 (q, J = 5.2 Hz, 1H), 3.29 (d, J = 5.6 Hz, 1H), 1.89 (s, 3H), 0.97 (s, 9H), 0.19 (s, 6H);
^{13}C NMR [125 MHz, $(CD_3)_2CO$)]: δ 140.3 (C), 128.8 (CH), 126.2 (CH), 120.9 (CH), 74.9 (CH), 69.4 (CH), 27.1 (CH_3), 21.2 (CH_3), 19.7 (C), -3.4 (CH_3), –4.0 (CH_3);
IR ν_{max} (KBr) 3564, 3457, 3044, 2954, 2930, 2887, 2857, 1472, 1463, 1442, 1404, 1389, 1374, 1361, 1309, 1253, 1218, 1156, 1109, 1090, 1051, 1035, 1004, 968, 938, 909, 881, 853, 837, 795, 776, 730, 700, 678 cm^{-1};
MS (ESI, +ve ion mode) *m/z*: 263 [$(M+Na)^+$, 100%], 223 (46), 165 (31), 102 (28), 91 (65), 73 (51);
HRESMS Found: $(M+Na)^+$, 263.1441. Calculated for $C_{13}H_{24}O_2Si$ $(M+Na)^+$, 263.1443.
Optical rotation $[\alpha]_D^{19}$ +34.8 (*c* 1, $CHCl_3$).

(*E*)-[(1*R*,6*S*)-6-(*tert*-Butyldimethylsilyloxy)-2-methylcyclohexa-2,4-dienyl] 3-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (100b).



80 **74a** **100b**

A solution of carboxylic acid **80**[4] (2.00 g, 11.62 mmol) in toluene (400 ml) was treated with triethylamine (1.76 g, 17.43 mmol, 1.5 eq) and 2,4,6-trichlorobenzoyl chloride (3.40 g, 13.94 mmol, 1.2 eq). The resulting solution was stirred at 18°C for 2 h. Meanwhile, in a separate flask, DMAP (1.28 g, 10.46 mmol, 0.9 eq) was added to a solution of monoprotected diol **74a** (2.51 g, 10.46 mmol, 0.9 eq) in toluene (135 ml). The resulting suspension was stirred at 18°C until a clear solution was obtained and which was then added, dropwise, to the reaction mixture containing the 2,4,6-trichlorobenzoyl anhydride of **80**. A solid started to form slowly, resulting in an initially slightly creamy mixture that eventually turned orange. After 20 h, TLC analysis showed that toluenediol **74a** had been completely consumed. Accordingly, the reaction was quenched with water (100 ml) and the separated aqueous phase was extracted with ethyl acetate (3 x 100 ml). The combined organic phases were then washed with brine (1 x 100 ml) before being dried (magnesium sulfate), filtered and concentrated under reduced pressure. The crude product was thus obtained as an orange oil (4.72 g) which could be used in the next step without further purification. For the purpose of spectroscopic characterisation, a small sample was subjected to column chromatography (silica, 1:9 v/v ethyl acetate/hexane). Concentration of the appropriate fractions then gave ester **100b** as a clear, colourless oil.

R_f = 0.4 in 1:9 v/v ethyl acetate/hexane;
^{1}H NMR (500 MHz, C_6D_6): δ 6.96 (dd, J = 15.4 and 5.1 Hz, 1H), 6.23 (dd, J = 15.4 and 1.5 Hz, 1H), 5.75-5.68 (complex m, 2H), 5.62 (d, J = 6.1 Hz, 1H), 5.62-5.59 (complex m, 1H), 4.55-4.51 (complex m, 1H), 4.17-4.12 (complex m, 1H), 3.57 (dd, J = 8.3 and 6.8 Hz, 1H), 3.23 (dd, J = 8.3 and 7.3 Hz, 1H), 1.73 (broad s, 3H), 1.24 (s, 3H), 1.22 (s, 3H), 0.95 (s, 9H), 0.12 (s, 3H), 0.06 (s, 3H);
^{13}C NMR (125 MHz, C_6D_6): δ 165.9 (C), 145.8 (CH), 133.8 (C), 129.2 (CH), 123.9 (CH), 122.9 (CH), 122.3 (CH), 110.0 (C), 75.1 (CH), 71.6 (CH), 69.2 (CH), 68.7 (CH_2), 26.4 (CH_3), 26.0 (CH_3), 25.9 (CH_3), 20.3 (CH_3), 18.4 (C), -4.8 (CH_3), -4.9 (CH_3);

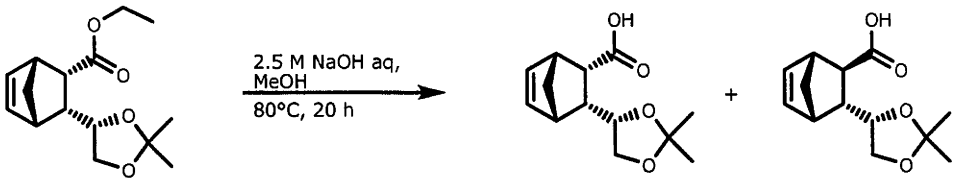
IR ν_{max} (KBr) 2987, 2956, 2930, 2883, 2857, 1722, 1661, 1300, 1256, 1215, 1165, 1109, 1064, 1036, 976, 838, 776 cm^{-1};

MS (ESI, +ve ion mode) *m/z*: 417 [$(M+Na)^+$, 61%], 223 (100), 195 (91), 165 (87), 73 (67);

HRESMS Found: $(M+Na)^+$, 417.2060. Calculated for $C_{21}H_{34}O_5Si$ $(M+Na)^+$, 417.2073.

Optical rotation $[\alpha]_D^{18}$ -61.4 (*c* 0.5, $CHCl_3$).

(1*R*,2*S*,3*R*,4*S*)-3-[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]bicyclo[2.2.1]hept-5-ene-2-carboxylic acid (108a) and (1*R*,2*R*,3*R*,4*S*)-3-[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]bicyclo[2.2.1]hept-5-ene-2-carboxylic acid (108b).



107 **108a** **108b**

Sodium hydroxide (2 ml of a 2.5 M aq. solution) was added to a solution of ester **107**[5] (145 mg, 0.54 mmol) in methanol (2 ml). The ensuing mixture was heated at 80°C for 20 h then cooled to room temperature and diluted with ethyl acetate (5 ml). The pH of the mixture was adjusted to around 5 using hydrochloric acid (1 M aq. solution). The separated aqueous phase was extracted with ethyl acetate (3 x 5 ml) then the combined organic layers were washed with brine (1 x 5 ml) before being dried (magnesium sulfate), filtered and concentrated under reduced pressure. The resulting clear, colourless oil (120 mg) was subjected to column chromatography (silica, eluent 1:1 v/v ethyl acetate/hexane) and concentration of the appropriate fractions then gave an inseparable 1:3 mixture of carboxylic acids **108a**[6] and **108b** (84 mg, 65%) as a clear, colourless oil.

R_f = 0.6 in 1:1 v/v ethyl acetate/hexane;
^{1}H NMR (300 MHz, $CDCl_3$): δ (compound **108b**) 6.23-6.20 (complex m, 2H), 3.94 (dd, J = 8.2 and 5.9 Hz, 1H), 3.74 (dd, J = 8.2 and 6.6 Hz, 1H), 3.54 (ddd, J = 9.9, 6.6 and 5.9 Hz, 1H), 3.12-3.07 (complex m, 2H), 2.47 (ddd, J = 9.9, 5.0 and 3.3 Hz, 1H), 1.71 (dd, J = 5.0 and 1.5 Hz, 1H), 1.63 (broad d, J = 8.8, 1 H), 1.50 (dd, J = 8.8 and 1.6 Hz, 1H), 1.43 (s, 3H), 1.33 (s, 3H), signal due to carboxylic acid proton not observed;
^{1}H NMR (300 MHz, $CDCl_3$): δ (compound **108a**) 6.30-6.23 (complex m, 2H), 4.02 (dd, J = 8.3 and 6.0 Hz, 1H), 3.85 (ddd, J = 10.8, 6.0 and 5.1 Hz, 1H), 3.69 (dd, J = 8.3 and 5.1 Hz, 1H), 3.19-3.13 (complex m, 2H), 3.06 (dd, J = 10.1 and 3.3 Hz, 1H), 2.54 (ddd, J = 10.8, 10.1 and 3.3 Hz, 1H, partly obscured), 1.52-1.46 (complex m, 1H), 1.45 (s, 3H), 1.36-1.32 (complex m, 1H), 1.30 (s, 3H), signal due to carboxylic acid proton not observed;
^{13}C NMR (75 MHz, $CDCl_3$): δ (compound **108b**) 180.9 (C), 136.5 (CH), 136.0 (CH), 109.0 (C), 79.0 (CH), 68.3 (CH_2), 48.1 (CH), 47.3 (CH_2), 46.9 (CH), 46.2 (CH), 44.5 (CH), 27.0 (CH_3), 25.7 (CH_3);

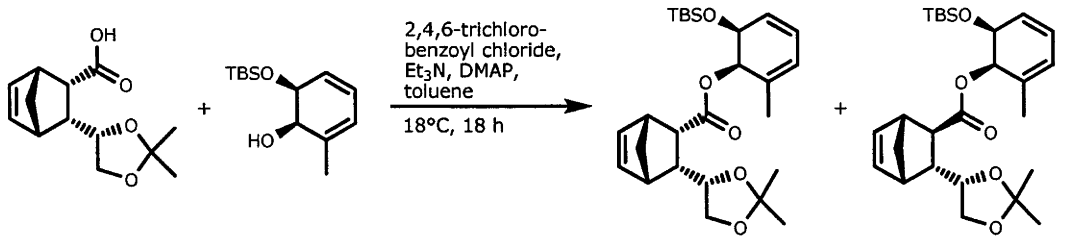
^{13}C NMR (75 MHz, $CDCl_3$): δ (compound **108a**) 135.7 (CH), 135.6 (CH), 108.2 (C), 77.1 (CH), 69.4 (CH_2), 49.3 (CH), 48.5 (CH_2), 47.0 (CH), 46.2 (CH), 46.0 (CH), 27.2 (CH_3), 25.1 (CH_3), signal due to carboxylic acid carbon not observed;

IR ν_{max} (KBr) 3063, 2986, 2938, 2877, 1732, 1703, 1455, 1417, 1380, 1371, 1336, 1284, 1253, 1214, 1157, 1071, 1056, 1032, 964, 916, 852, 789, 729, 676, 512 cm^{-1};

MS (EI, 70 eV) *m/z*: 238 ($M^{+\bullet}$, 8%), 223 [$(M\text{-}CH_3\bullet)^+$, 62], 117 (54), 97 (51), 91 (51), 72 (52), 66 (99), 43 (100);

HREIMS Found: $M^{+\bullet}$, 238.1203. Calculated for $C_{13}H_{18}O_4$ $M^{+\bullet}$, 238.1205.

(1*R*,2*S*,3*R*,4*S*)-[(1*R*,6*S*)-6-(*tert*-Butyldimethylsilyloxy)-2-methylcyclohexa-2,4-dienyl] 3-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]bicyclo[2.2.1]hept-5-ene-2-carboxylate (109a) and (1*R*,2*S*,3*R*,4*S*)-[(1*R*,6*S*)-6-(*tert*-Butyldimethylsilyloxy)-2-methylcyclohexa-2,4-dienyl] 3-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]bicyclo[2.2.1]hept-5-ene-2-carboxylate (109b).



108a **74a** **109a** **109b**

Triethylamine (64 mg, 0.63 mmol, 1.5 eq) was added to a solution of carboxylic acid **108a** (100 mg, 0.42 mmol) in toluene (14 ml). The resulting mixture was treated with 2,4,6-trichlorobenzoyl chloride (122 mg, 0.50 mmol, 1.2 eq) then stirred at 18°C for 2 h. Meanwhile, in a separate flask, monoprotected diol **74a** (91 mg, 0.38 mmol, 0.9 eq) was dissolved in toluene (4.9 ml), and DMAP (46 mg, 0.38 mmol, 0.9 eq) was added. The resulting mixture was stirred at 18°C until the solids had dissolved and then added dropwise to the reaction mixture containing the 2,4,6-trichlorobenzoyl anhydride of **108a**. After 16 h, the reaction was quenched with water (2 ml) and the separated aqueous phase extracted with ethyl acetate (3 x 5 ml). The combined organic phases were washed with brine (1 x 10 ml) before being dried (magnesium sulfate), filtered and concentrated under reduced pressure. The ensuing orange oil was subjected to column chromatography (silica, eluent 1:9 v/v ethyl acetate/hexane) and concentration of the appropriate fractions then gave a 1.2:1 and inseparable mixture of esters **109a** and **109b** (155 mg, 89%) as a clear, colourless oil.

R_f = 0.7 and 0.6 in 1:4 v/v ethyl acetate/hexane;
^{1}H NMR (300 MHz, C_6D_6): δ 6.51 (dd, J = 5.5 and 2.9 Hz, 1H), 6.37 (dd, J = 5.5 and 2.9 Hz, 1H), 6.12 (dd, J = 5.5 and 2.9 Hz, 1H), 5.87 (dd, J = 5.5 and 2.9 Hz, 1H), 5.68 (dd, J = 4.5 and 3.2 Hz, 4H), 5.62-5.55 (complex m, 2H), 5.42 (d, J = 6.0 Hz, 1H), 5.27 (d, J = 6.0 Hz, 1H), 4.54 (d, J = 6.0 Hz, 1H), 4.49 (d, J = 6.0 Hz, 1H), 4.25 (dd, J = 8.2 and 5.9 Hz, 1H), 4.09-3.94 (complex m, 3H), 3.80 (dd, J = 8.2 and 5.2 Hz, 1H), 3.45 (ddd, J = 10.0, 7.4 and 5.9 Hz, 1H), 3.21 (broad s, 2H), 3.11 (broad s, 1H), 3.04 (broad s, 1H), 2.81 (dd, J = 9.9 and 3.4 Hz, 1H), 2.66 (ddd, J = 10.0, 4.8 and 3.6 Hz, 1H), 2.30 (dt, J = 10.0 and 3.3 Hz, 1H), 1.85 (d, J

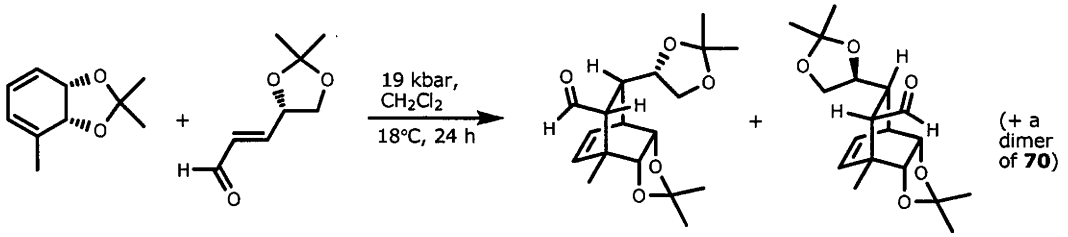
= 8.4 Hz, 1H), 1.72-1.30 (complex m, hidden under other signals, 4H), 1.70 (broad s, 3H), 1.66 (broad s, 3H), 1.49 (s, 3H), 1.48 (s, 3H), 1.34 (s, 3H), 1.32 (s, 3H), 0.95 (s, 18H), 0.09 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H), 0.04 (s, 3H);

IR ν_{max} (KBr) 2984, 2955, 2932, 2883, 2857, 1732, 1378, 1368, 1252, 1212, 1183, 1159, 1107, 1070, 1051, 1005, 967, 889, 846, 839, 813, 777 cm^{-1};

MS (ESI, +ve ion mode) *m/z*: 483 [$(M+Na)^+$, 59%], 261 (100), 115 (24), 97 (28);

HRESMS Found: $(M+Na)^+$, 483.2546. Calculated for $C_{26}H_{40}O_5Si$ $(M+Na)^+$, 483.2543.

(3a*S*,4*S*,7*R*,7a*R*,8*R*,9*S*)-9-[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3a,4,7,7a-tetrahydro-2,2,7-trimethyl-4,7-ethano-1,3-benzodioxole-8-carbaldehyde (124a) and (3a*S*,4*S*,7*R*,7a*R*,8*S*,9*R*)-9-[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3a,4,7,7a-tetrahydro-2,2,7-trimethyl-4,7-ethano-1,3-benzodioxole-8-carbaldehyde (124b)



70 **123** **124a** **124b**

A solution of aldehyde **123**[7] (644 mg, 4.13 mmol, 1 eq) and toluenediol **70** (686 mg, 4.13 mmol, 1 eq) in dichloromethane (16 ml) was pressurised, at 18°C, to 19 kbar in a PSIKA high pressure reactor. After 24 h the pressure was released and the reaction mixture concentrated under reduced pressure to give a 2.4:2.4:1.4:1 mixture of **124a**, **124b**, **123** and a dimer of **70**. This material was subjected to column chromatography (silica, 1:4 v/v ethyl acetate/hexane) to afford three fractions, A, B and C.

Concentration of fraction A (R_f = 0.4 in 1:4 v/v ethyl acetate/hexane) afforded a Diels-Alder dimer of **70** (139 mg, 10%) as a clear, colourless oil. The spectral data derived from this material were identical with those reported previously.[8]

Concentration of fraction B (R_f = 0.3 in 1:4 v/v ethyl acetate/hexane) gave an inseparable 1:1 mixture of the two product isomers **124a** and **124b** (799 mg, 60%).

Concentration of fraction C (R_f = 0.2 in 1:4 v/v ethyl acetate/hexane) afforded starting material **123** (172 mg, 27%) as a clear, colourless oil with identical spectral properties as previously obtained material.

A sample of fraction B (60 mg) was subjected to reverse phase high-pressure liquid chromatography (AECS C18/4μm column, 40% acetonitrile in water) to afford, after extractive work-up with ethyl acetate, fractions D and E.

Concentration of the extract derived from fraction D afforded a yellowish oil that was subjected to flash column chromatography (silica, 1:4 v/v ethyl acetate/ hexane) to yield aldehyde **124b** (15 mg) as a clear, colourless oil.

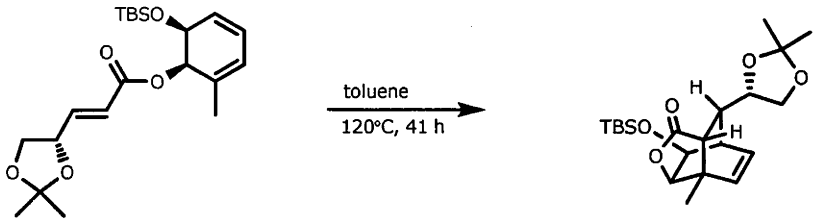
^{1}H NMR (300 MHz, $CDCl_3$): δ 9.86 (d, J = 2.6 Hz, 1H), 6.07 (dd, J = 8.2 and 6.5 Hz, 1H), 5.85 (dt, J = 8.2 and 1.2 Hz, 1H), 4.27 (ddd, J = 7.2, 3.3 and 0.8 Hz, 1H), 3.98 (dd, J = 7.2 and 1.4 Hz, 1H), 3.84-3.72 (complex m, 2H), 3.45-3.41 (complex m, 1H), 3.17-3.13 (complex m, 1H), 2.29-2.24 (complex m, 1H), 1.80 (dd, J = 5.9 and 2.6 Hz, 1H), 1.46 (s, 3H), 1.38 (s, 3H), 1.30 (s, 6H), 1.24 (s, 3H);
^{13}C NMR (75 MHz, $CDCl_3$): δ 202.5 (CH), 136.1 (CH), 130.0 (CH), 109.0 (C), 108.6 (C), 79.6 (CH), 78.9 (CH), 77.8 (CH), 67.0 (CH_2), 56.1 (CH), 41.8 (C), 38.5 (CH), 37.0 (CH), 26.8 (CH_3), 25.5 (CH_3), 25.3 (CH_3), 24.9 (CH_3), 19.5 (CH_3);
IR ν_{max} (KBr) 2985, 2935, 2878, 1718, 1380, 1372, 1258, 1232, 1209, 1164, 1124, 1068, 895, 876, 858, 839, 728, 508 cm^{-1};
MS (ESI, +ve ion mode) *m/z*: 345 [$(M+Na)^+$, 100%], 323 [$(M+H)^+$, <1];
HRESMS Found: $(M+Na)^+$, 345.1678. Calculated for $C_{18}H_{26}O_5$ $(M+Na)^+$, 345.1678.
Optical rotation $[\alpha]_D^{20}$ +34.8 (*c* 0.75, $CHCl_3$).

Concentration of the extract derived from fraction E afforded a yellow oil that was subjected to flash column chromatography (silica, 1:4 v/v ethyl acetate/hexane) to yield aldehyde **124a** (14 mg) as a clear, colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.52 (d, J = 3.4 Hz, 1H) 6.24 (ddd, J = 8.2, 6.6 and 0.7 Hz, 1H), 5.75 (d, J = 8.2 Hz, 1H), 4.57 (dd, J = 7.1 and 3.4 Hz, 1H), 4.11 (dt, J = 7.5 and 6.0 Hz, 1H), 4.02 (dd, J = 8.3 and 6.0 Hz, 1H), 3.89 (dd, J = 7.1 and 1.0 Hz, 1H), 3.52 (dd, J = 8.3 and 7.5 Hz, 1H), 2.84-2.81 (complex m, 1H), 2.23 (dd, J = 5.6 and 3.4 Hz, 1H), 2.04 (ddd, J = 6.0, 5.6 and 2.7 Hz, 1H), 1.39 (s, 3H), 1.36 (s, 3H), 1.33 (s, 3H), 1.30 (s, 3H), 1.27 (s, 3H);
^{13}C NMR (125 MHz, $CDCl_3$): δ 202.9 (CH) 133.2 (CH), 132.6 (CH), 109.3 (C), 108.5 (C), 82.5 (CH), 77.1 (CH), 75.6 (CH), 68.0 (CH_2), 54.2 (CH), 41.3 (C), 40.1 (CH), 38.6 (CH), 26.5 (CH_3), 25.6 (CH_3), 25.4 (CH_3), 25.1 (CH_3), 19.3 (CH_3);
IR ν_{max} (KBr) 2985, 2936, 2877, 1723, 1457, 1378, 1372, 1260, 1209, 1163, 1114, 1086, 1064, 990, 965, 883, 851, 809, 729, 511 cm^{-1};
MS (ESI, +ve ion mode) *m/z*: 345 [$(M+Na)^+$, 100%), 207 (21), 119 (18);
HRESMS Found: $(M+Na)^+$, 345.1676. Calculated for $C_{18}H_{26}O_5$ $(M+Na)^+$, 345.1678.
Optical rotation $[\alpha]_D^{19}$ +6.2 (*c* 0.65, $CHCl_3$).

5.3 Experimental procedures associated with work described in Chapter 3

(3*R*,3a*S*,6*R*,7*S*,7a*R*,8*S*)-7-*tert*-Butyldimethylsiloxy-8-[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-2,3,3a,6,7,7a-hexahydro-3a-methyl-2-oxo-3,6-methano-benzofuran (105b).



100b **105b**

The crude orange oil containing compound **100b** (4.72 g) that was obtained as described in the previous step was dissolved in toluene (70 ml) and the resulting solution was heated to 120°C. After 41 h, TLC analysis showed that no starting material remained. Accordingly, the reaction mixture was allowed to cool, and the solvent was removed under reduced pressure. The resulting orange oil was subjected to column chromatography (silica, 1:4 v/v ethyl acetate/hexane). Concentration of the appropriate fractions then gave the Diels-Alder adduct **105b** (2.80 g, 68% over two steps) as a white, crystalline solid, m.p. 122-127°C.

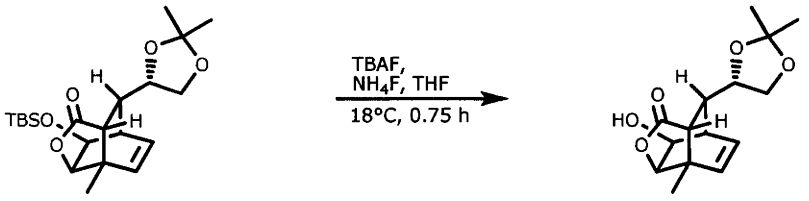
R_f = 0.4 in 1:4 v/v ethyl acetate/hexane;
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.24 (dd, J = 8.2 and 7.1 Hz, 1H), 5.84 (dd, J = 8.2 and 1.2 Hz, 1H), 3.97 (dd, J = 8.1 and 6.2 Hz, 1H), 3.81 (dd, J = 6.8 and 1.5 Hz, 1H), 3.78 (dt, J = 9.4 and 6.2 Hz, 1H), 3.58 (dd, J = 8.1 and 6.2 Hz, 1H), 3.54 (dd, J = 6.8 and 2.4 Hz, 1H), 2.47 (broad ddd, J = 9.4, 2.4 and 1.7 Hz, 1H), 2.44-2.41 (complex m, 1H), 2.30-2.28 (complex m, 1H), 1.42 (s, 3H), 1.39 (s, 3H), 1.30 (s, 3H), 0.90 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H);
^{13}C NMR (125 MHz, $CDCl_3$): δ 178.9 (C), 133.2 (CH), 132.2 (CH), 109.3 (C), 78.3 (CH), 76.7 (CH), 69.3 (CH), 68.1 (CH_2), 46.8 (CH), 45.2 (C), 43.0 (CH), 42.2 (CH), 26.9 (CH_3), 25.8 (CH_3), 25.7 (CH_3), 20.8 (CH_3), 18.1 (C), -4.8 (CH_3), -5.1 (CH_3);
IR ν_{max} (KBr) 2982, 2953, 2930, 2886, 2857, 1784, 1472, 1462, 1378, 1370, 1339, 1252, 1222, 1159, 1151, 1131, 1105, 1073, 1029, 1015, 1002, 957, 878, 838, 807, 777, 715 cm^{-1};
MS (ESI, +ve ion mode) *m/z*: 417 [$(M+Na)^+$, 100%], 395 [$(M+H)^+$, 65], 394 ($M^{+\cdot}$, <1), 337 {[$M-(CH_3)_3C\cdot]^+$, 56};

HRESMS Found: $(M+Na)^+$, 417.2073. Calculated for $C_{21}H_{34}O_5Si$ $(M+Na)^+$, 417.2073.

Elemental analysis Found: C, 64.12; H, 8.18; $C_{21}H_{34}O_5Si$ requires: C, 63.92; H, 8.68%;

Optical rotation $[\alpha]_D^{18}$ -28.6 (*c* 0.8, $CHCl_3$).

(3*R*,3a*S*,6*R*,7*S*,7a*R*,8*S*)-8-[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-2,3,3a,6,7, 7a-hexahydro-7-Hydroxy-3a-methyl-2-oxo-3,6-methanobenzofuran (131).



105b **131**

A solution of Diels-Alder adduct **105b** (1.00 g, 2.54 mmol) in THF (232 ml) was treated with ammonium fluoride[7] (470 mg, 12.70 mmol, 5 eq) and TBAF (12.70 ml of a 1 M solution in THF, 12.70 mmol, 5 eq). The resulting mixture was stirred at 18°C and after 0.6 h no more starting material could be detected by TLC. Accordingly, and after a total reaction time of 0.75 h, the reaction mixture was poured into a mixture of brine (15 ml) and ethyl acetate (15 ml). The separated aqueous phase was extracted with ethyl acetate (3 x 15 ml) and the combined organic layers were dried (magnesium sulfate), filtered and concentrated under reduced pressure. The residual yellow oil was subjected to column chromatography (silica, eluent 1:1 v/v ethyl acetate/dichloromethane) and concentration of the appropriate fractions then gave alcohol **131** (657 mg, 92%) as a white, gummy solid, m.p. 37-41°C.

R_f = 0.4 in 1:1 v/v ethyl acetate/dichloromethane;

^{1}H NMR (500 MHz, $(CD_3)_2CO$): δ 6.41 (dd, J = 8.2 and 7.1 Hz, 1H), 5.93 (dd, J = 8.2 and 1.2 Hz, 1H), 4.23 (d, J = 4.9 Hz, 1H), 4.05 (dd, J = 8.3 and 6.1 Hz, 1H), 4.01 (dd, J = 6.7 and 1.2 Hz, 1H), 3.80 (dt, J = 9.8 and 6.1 Hz, 1H), 3.65 (dd, J = 8.3 and 6.1 Hz, 1H), 3.59 (ddd, J = 6.7, 5.3 and 2.3 Hz, 1H), 2.67-2.65 (complex m, 1H), 2.47 (ddd, J = 9.8, 2.7 and 1.8 Hz, 1H), 2.21 (t, J = 1.8 Hz, 1H), 1.41 (s, 3H), 1.38 (s, 3H), 1.28 (s, 3H);

^{13}C NMR (125 MHz, $(CD_3)_2CO$): δ 179.6 (C), 135.8 (CH), 133.2 (CH), 110.2 (C), 80.1 (CH), 78.6 (CH), 70.3 (CH), 69.4 (CH_2), 48.5 (CH), 46.4 (C), 44.7 (CH), 42.7 (CH), 28.1 (CH_3), 26.8 (CH_3), 21.7 (CH_3);

IR ν_{max} (KBr) 3451, 2983, 2934, 2877, 1779, 1456, 1380, 1371, 1338, 1247, 1221, 1163, 1152, 1116, 1070, 1024, 1011, 990, 956, 893, 848, 796, 714, 511 cm^{-1};

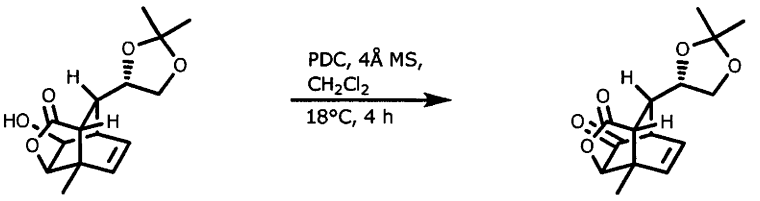
MS (EI, 70 eV) *m/z*: 280 ($M^{+\cdot}$, 6%), 265 [$(M\text{-}CH_3\cdot)^+$, 71], 135 (74), 119 (84), 105 (75), 101 (72), 91 (73), 43 (100), 41 (74);

HREIMS Found: $M^{+\cdot}$, 280.1314. Calculated for $C_{15}H_{20}O_5$ $M^{+\cdot}$, 280.1311.

Optical rotation $[\alpha]_D^{18}$ +21.6 (*c* 1, $CHCl_3$);

Elemental analysis Found C, 64.10; H, 7.00; $C_{15}H_{20}O_5$ requires: C, 64.27; H, 7.19%.

(3*R*,3a*S*,6*R*,7a*R*,8*S*)-8-[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-2,3,3a,6,7,7a-hexahydro-3a-methyl-2,7-dioxo-3,6-methanobenzofuran (132).



131 **132**

Alcohol **131** (478 mg, 1.71 mmol), PDC (3.217 g, 8.55 mmol, 5 eq) and freshly activated 4 Å molecular sieves (1.71 g) were combined in a flask, and a nitrogen atmosphere was established. After the addition of dichloromethane, the mixture was stirred at 18°C for 4 h then diluted with diethyl ether (15 ml) and filtered through a short plug of Celite™. The latter was flushed with diethyl ether and the combined filtrates were concentrated under reduced pressure. The orange/white semi-solid oil (359 mg) thus obtained was subjected to column chromatography (silica, 1:4 -> 1:2 v/v ethyl acetate/hexane) and concentration of the appropriate fractions then gave ketone **132** (323 mg, 68%) as a white, crystalline solid, m.p. 146-153°C.

R_f = 0.3 in 1:2 v/v ethyl acetate/hexane;

^{1}H NMR (500 MHz, $(CD_3)_2CO$): δ 6.49 (dd, J = 8.2 and 6.7 Hz, 1H), 6.29 (dd, J = 8.2 and 1.2 Hz, 1H), 4.09 (dd, J = 8.5 and 5.9 Hz, 1H), 3.98 (s, 1H), 3.96 (ddd, J = 9.5, 5.9 and 5.6 Hz, 1H), 3.83 (dd, J = 8.5 and 5.6 Hz, 1H), 3.38 (dd, J = 6.7 and 3.2 Hz, 1H), 2.67 (broad s, 1H), 2.50 (dd, J = 9.5 and 3.2 Hz, 1H), 1.53 (s, 3H), 1.40 (s, 3H), 1.31 (d, J = 0.5 Hz, 3H);

^{13}C NMR (125 MHz, $(CD_3)_2CO$): δ 200.2 (C), 178.7 (C), 137.1 (CH), 130.9 (CH), 110.5 (C), 80.0 (CH), 76.7 (CH), 69.0 (CH_2), 51.2 (CH), 48.3 (CH), 47.9 (CH), 47.5 (C), 27.9 (CH_3), 26.8 (CH_3), 20.3 (CH_3);

IR ν_{max} (KBr) 2985, 1793, 1749, 1383, 1372, 1306, 1249, 1220, 1154, 1109, 1098, 1071, 1049, 1000, 871, 847, 833, 813, 714, 510, 492 cm^{-1};

MS (EI, 70 eV) *m/z*: 278 ($M^{+\bullet}$, 8%), 263 [$(M-CH_3\bullet)^+$, 87], 250 (69), 135 (59), 119 (89), 101 (68), 43 (100);

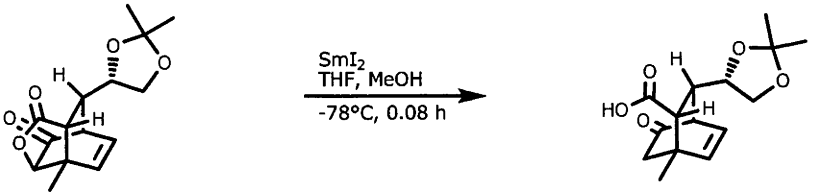
HREIMS Found: $M^{+\bullet}$, 278.1151. Calculated for $C_{15}H_{18}O_5$ $M^{+\bullet}$, 278.1154.

Optical rotation $[\alpha]_D^{18}$ -277.6 (*c* 0.7, $CHCl_3$);

Elemental analysis Found: C, 64.82; H, 6.34; $C_{15}H_{18}O_5$ requires: C, 64.74; H, 6.52%.

A sample was recrystallised (hexane/benzene) and subjected to single-crystal X-ray analysis.

(1*S*,2*R*,3*S*,4*R*)-3-[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-1-methyl-5-oxo-bicyclo[2.2.2]oct-7-ene-2-carboxylic acid (133).

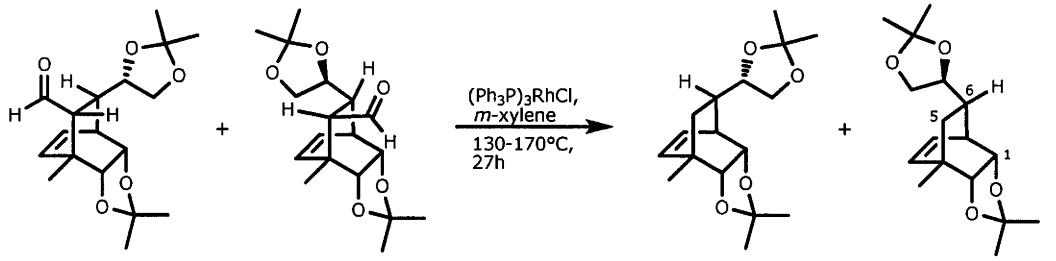


132 **133**

A magnetically stirred solution of ketone **132** (61 mg, 219 μmol) in THF (2.2 ml) and methanol (1.1 ml) was cooled to -78°C then samarium diiodide (4.8 ml of a 0.1 M solution in THF, *ca.* 0.48 mmol, 2.2 eq.) was added dropwise until a dark blue-green colour persisted. The reaction mixture was stirred at -78°C for 0.08 h, and then quenched with potassium carbonate (7 ml of a saturated aq. solution) and diluted with ethyl acetate (20 ml). The heterogeneous mixture thus obtained was stirred thoroughly while being treated with hydrochloric acid (a 37% aq. solution) until a pH of 5 was obtained. The separated aqueous layer was extracted with ethyl acetate (3 x 20 ml) and the combined organic phases were washed successively with water (1 x 10 ml) and brine (1 x 10 ml) before being dried (magnesium sulfate), filtered and concentrated under reduced pressure. The yellow oil thus obtained (38 mg) was subjected to column chromatography (silica, 1:4 v/v ethyl acetate/hexane) and concentration of the appropriate fractions then gave carboxylic acid **133** (16 mg, 26%) as a clear, colourless oil.

R_f = 0.3 in 1:4 v/v ethyl acetate/hexane;
^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 6.35 (dd, J = 8.0 and 1.1 Hz, 1H), 6.21 (dd, J = 8.0 and 6.6 Hz, 1H), 4.11 (dd, J = 8.3 and 5.8 Hz, 1H), 3.84 (ddd, J = 9.2, 5.8 and 5.6 Hz, 1H), 3.75 (dd, J = 8.3 and 5.6 Hz, 1H), 2.98 (dt, J = 6.6 and 1.4 Hz, 1H), 2.57-2.52 (complex m, 1H), 2.51 (d, J = 18.4 Hz, 1H), 2.43 (broad d, J = 5.6 Hz, 1H), 1.77 (dd, J = 18.4 and 1.9 Hz, 1H), 1.36 (s, 3H), 1.31 (split s, J = 0.3 Hz, 3H), 1.27 (broad s, 3H);
^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ 209.5 (C), 144.2 (CH), 127.6 (CH), 110.2 (C), 80.2 (CH), 69.3 (CH_2), 52.6 (CH), 46.8 (CH), 42.3 (CH_2), 41.4 (C), 27.7 (CH_3), 26.5 (CH_3), 23.1 (CH_3), signal due to carboxylic acid carbon not observed;
IR ν_{max} (KBr) 3051, 2985, 2934, 2878, 1730, 1703, 1455, 1402, 1381, 1372, 1357, 1284, 1253, 1213, 1189, 1152, 1114, 1069, 1057, 1032, 848, 7091284, 1253, 1213, 1189, 1152, 1114, 1069, 1057, 1032, 848, 709 cm^{-1};
MS (ESI, +ve ion mode) *m/z*: 279 [$(M-H)^-$, 100%];
HRESMS Found: $(M-H)^-$, 279.1231. Calculated for $C_{15}H_{20}O_5$ $(M-H)^-$, 279.1232.

(3a*S*,4*S*,7*S*,7a*R*,9*S*)-9-[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3a,4,7,7a-tetrahydro-2,2,7-trimethyl-4,7-ethano-1,3-benzodioxole (134b).



124a **124b** **134a** **134b**

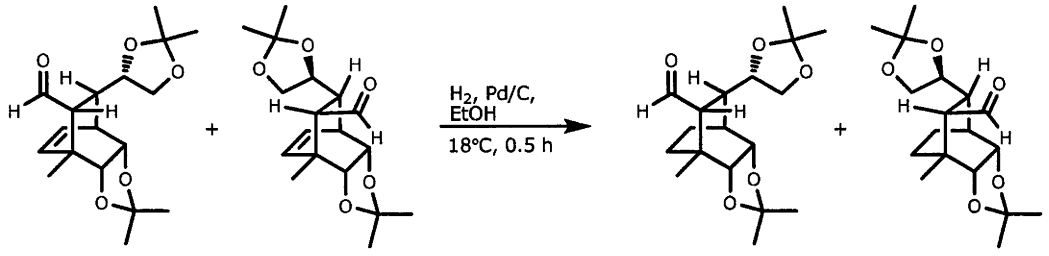
A 1:1 mixture of aldehydes **124a** and **124b** (32 mg, 0.10 mmol) in *m*-xylene (3 ml) was treated with chlorotris(triphenylphosphine)rhodium(I) (148 mg, 0.16 mmol, 1.6 eq). The reaction mixture was gently degassed, flushed with nitrogen before being heated at 130°C for 19 h, at 150°C for 3 h and then at 170°C for 5 h. The cooled reaction mixture was then filtered through a plug of cotton wool and the filtrate subjected to flash column chromatography (silica, 1:4 v/v ethyl acetate/hexane) to afford two fractions, A and B.

Concentration of fraction A (R_f = 0.4 in 1:4 v/v ethyl acetate/hexane) afforded olefin **134b** (14 mg) as a light-yellow oil that was contaminated with traces of triphenylphosphine and isomer **134a**.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.99 (dd, J = 8.2 and 6.6 Hz, 1H), 5.86 (d, J = 8.2 Hz, 1H), 4.23 (dd, J = 7.3 and 3.4 Hz, 1H), 3.92 (dd, J = 8.1 and 6.0 Hz, 1H), 3.82 (d, J = 7.3 Hz, 1H), 3.69 (dt, J = 9.5 and 6.0 Hz, 1H), 3.57 (dd, J = 8.1 and 6.0 Hz, 1H), 3.11-3.08 (complex m, 1H), 1.76-1.70 (complex m, 1H), 1.40 (s, 3H), 1.31 (dd, J = 13.2 and 3.4 Hz, 1H, partially obscured), 1.31 (s, 6H), 1.27 (s, 3H), 1.21 (s, 3H), 0.56 (dd, J = 13.2 and 5.1 Hz, 1H);
^{13}C NMR (125 MHz, $CDCl_3$): δ 136.5 (CH), 128.6 (CH), 108.9 (C), 108.2 (C), 82.8 (CH), 79.6 (CH), 78.5 (CH), 67.8 (CH_2), 38.7 (CH), 38.2 (C), 36.8 (CH), 32.7 (CH_2), 27.1 (CH_3), 25.6 (CH_3), 25.5 (CH_3), 24.9 (CH_3), 21.7 (CH_3);
MS (ESI, +ve ion mode) *m/z*: 317 [$(M+Na)^+$, 22%], 294 ($M^{+\bullet}$, 24), 198 (100), 133 (87), 105 (83), 74 (82).

Concentration of fraction B (R_f = 0.3 in 1:4 v/v ethyl acetate/hexane) afforded compound **124b** (7 mg, 22%) as a clear, colourless oil. This material was identical, in all respects, with an authentic sample

(3a*S*,4*S*,7*R*,7a*R*,8*R*,9*S*)-9-[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3a,4,5,6,7,7a-hexahydro-2,2,7-trimethyl-4,7-ethano-1,3-benzodioxole-8-carbaldehyde (138a) and (3a*S*,4*S*,7*R*,7a*R*,8*S*,9*R*)-9-[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3a,4,5,6,7,7a-hexahydro-2,2,7-trimethyl-4,7-ethano-1,3-benzodioxole-8-carbaldehyde (138b)



124a **124b** **138a** **138b**

A solution of the 1:1 mixture of aldehydes **124a** and **124b** (100 mg, 0.31 mmol) in ethanol (1.1 ml) was treated with palladium black (20 mg) then a hydrogen atmosphere was established over the heterogeneous mixture which was stirred at 18°C for 0.5 h. The reaction mixture was then filtered through a 2 cm deep plug of Celite™ sitting on top of a 4 cm column of TLC-grade silica. Concentration of the filtrate gave an inseparable 1:1 mixture of isomers **138a** and **138b** (86 mg) as a clear, colourless oil. Most of the oil (83 mg) was subjected to high-pressure chromatography (AECS C18/4μm column, 1:1 v/v water/acetonitrile) to afford two fractions A and B that were separately treated as follows. The respective fraction was extracted with ethyl acetate. The combined organic layers were washed with brine then dried (magnesium sulfate), filtered and concentrated under reduced pressure.

Concentration of fraction A afforded aldehyde **138b** (39 mg, 39%) as a yellowish solid. For characterisation purposes the solid was repurified by flash column chromatography (silica, 1:4 v/v ethyl acetate/hexane) to yield **138b** (21 mg) as a white, crystalline solid, m.p. 96-98°C.

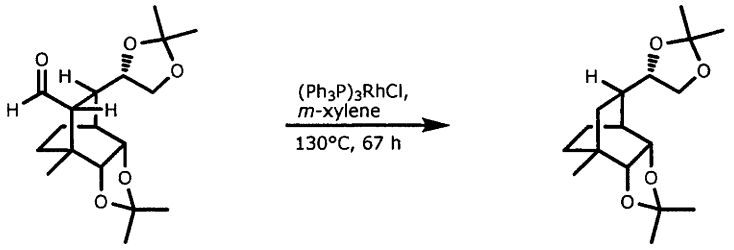
R_f = 0.4 in 1:4 v/v ethyl acetate/hexane;
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.83 (d, J = 2.4 Hz, 1H), 4.12 (ddd, J = 8.1, 3.7 and 1.0 Hz, 1H), 4.02 (ddd, J = 9.0, 6.6 and 5.9 Hz, 1H), 3.95 (dd, J = 8.1 and 5.9 Hz, 1H), 3.84 (dd, J = 8.1 and 1.7 Hz, 1H), 3.45 (dd, J = 8.1 and 6.6 Hz, 1H), 2.27-2.24 (complex m, 1H), 2.20-2.16 (complex m, 1H), 1.96 (dd, J = 6.6 and 2.4 Hz, 1H), 1.85-1.78 (complex m, 1H), 1.76-1.71 (complex m, 1H), 1.50-1.44 (complex m, 1H), 1.48 (s, 3H), 1.38 (s, 3H), 1.33 (s, 3H), 1.31 (s, 3H), 1.12 (s, 3H), 1.06-1.00 (complex m, 1H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 203.24 (CH), 203.2 (CH), 109.2 (C), 108.3 (C), 77.0 (CH), 76.8 (CH), 75.7 (CH), 67.8 (CH_2), 57.0 (CH), 36.4 (C), 36.2 (CH), 30.3 (CH), 27.2 (CH_2), 26.9 (CH_3), 25.7 (CH_3), 25.7 (CH_3), 24.1 (CH_3), 22.0 (CH_3), 13.9 (CH_2);
IR ν_{max} (KBr) 2985, 2956, 2938, 2909, 2878, 1719, 1468, 1458, 1380, 1371, 1262, 1245, 1208, 1165, 1137, 1069, 1032, 880, 867, 849, 839, 510 cm^{-1};
MS (ESI, +ve ion mode) *m/z*: 347 [$(M+Na)^+$, 100%], 325 [$(M+H)^+$, <1];
HRESMS Found: $(M+Na)^+$, 347.1835. Calculated for $C_{18}H_{28}NO_5$ $(M+Na)^+$, 347.1834.
Elemental analysis Found C, 66.41; H, 8.59; $C_{18}H_{28}O_5$ requires: C, 66.64; H, 8.70%;
Optical rotation $[\alpha]_D^{21}$ +101.0 (*c* 0.9, $CHCl_3$).

Concentration of fraction B afforded crude samples of aldehyde **138a** (31 mg, 31%) as a light-yellow oil. For the purpose of full characterisation the oil was repurified by flash column chromatography (silica, 1:4 v/v ethyl acetate/hexane) to yield **138a** (20 mg) as a clear, colourless oil.

R_f = 0.4 in 1:4 v/v ethyl acetate/hexane;
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.89 (d, J = 2.2 Hz, 1H), 4.37 (dd, J = 8.1 and 3.7 Hz, 1H), 4.04-3.98 (complex m, 2H), 3.82 (dd, J = 8.1 and 1.7 Hz, 1H), 3.50-3.45 (complex m, 1H), 2.49-2.45 (complex m, 1H), 2.30 (dt, J = 6.2 and 2.2 Hz, 1H), 1.96-1.89 (complex m, 1H), 1.83-1.81 (complex m, 1H), 1.59-1.53 (complex m, 1H), 1.48 (s, 3H), 1.35 (s, 3H), 1.34 (s, 3H), 1.30 (s, 3H), 1.27-1.20 (complex m, 1H), 1.14-1.08 (complex m, 1H), 1.11 (s, 3H);
^{13}C NMR (125 MHz, $CDCl_3$): δ 203.7 (CH), 203.7 (CH), 109.1 (C), 108.5 (C), 79.6 (CH), 77.7 (CH), 72.7 (CH), 68.0(CH_2), 54.1 (CH), 38.8 (CH), 36.2 (C), 32.5 (CH), 26.5 (CH_3), 25.7 (CH_3), 25.5 (CH_3), 24.3 (CH_3), 21.6 (CH_3), 21.5 (CH_2), 19.7 (CH_2);
IR ν_{max} (KBr) 2985, 2965, 2936, 2909, 2874, 1723, 1466, 1458, 1380, 1372, 1264, 1249, 1209, 1162, 1061, 1016, 879, 850, 513 cm^{-1};
MS (ESI, +ve ion mode) *m/z*: 347 [$(M+Na)^+$, 100%], 209 (32), 191 (39);
HRESMS Found: $(M+Na)^+$, 347.1832. Calculated for $C_{18}H_{28}O_5$ $(M+Na)^+$, 347.1834.
Optical rotation $[\alpha]_D^{21}$ -46.6 (*c* 1, $CHCl_3$).

(3a*S*,4*S*,7*R*,7a*R*,9*R*)-9-[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3a,4,5,6,7,7a-hexahydro-2,2,7-trimethyl-4,7-ethano-1,3-benzodioxole (139a)



138a **139a**

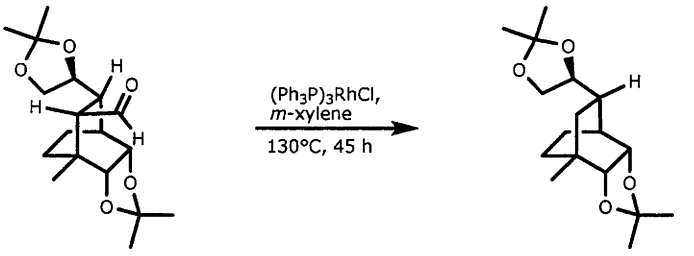
A solution of aldehyde **138a** (19 mg, 0.06 mmol) in *m*-xylene (2.2 ml) was added to Wilkinson's catalyst (93 mg, 0.10 mmol, 1.6 eq). The ensuing heterogeneous mixture was heated at 130°C for 67 h then cooled to room temperature and filtered through a small plug of Celite™. The plug was washed with some ethyl acetate and the combined filtrates concentrated under reduced pressure to yield a yellow oil. The latter was diluted with a small amount of eluent and subjected to column chromatography (silica, 1:4 v/v ethyl acetate/hexane). Two fractions, A and B, were obtained.

Concentration of fraction A (R_f = 0.5 in 1:4 v/v ethyl acetate/hexane) afforded adduct **139a** (5 mg, 29%) as a clear, colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.31 (dd, J = 8.3 and 2.7 Hz, 1H), 4.04-3.98 (complex m, 2H), 3.75 (dd, J = 8.3 and 1.5 Hz, 1H), 3.56-3.50 (complex m, 1H), 1.97-1.86 (complex m, 2H), 1.67-1.55 (complex m, 3H), 1.49 (s, 3H), 1.41 (s, 3H), 1.35 (s, 3H), 1.34 (s, 3H), 1.23-1.16 (complex m, 2H), 1.09-1.02 (complex m, 1H), 0.90 (s, 3H);
^{13}C NMR (125 MHz, $CDCl_3$): δ 108.9 (C), 107.6 (C), 80.1 (CH), 79.2 (CH), 72.9 (CH), 68.4 (CH_2), 38.7 (CH), 34.3 (CH_2), 33.0 (CH), 31.9 (C), 26.8 (CH_3), 25.8 (CH_3), 25.7 (CH_3), 24.8 (CH_2), 24.7 (CH_3), 24.2 (CH_3), 20.4 (CH_2);
IR ν_{max} (KBr) 2985, 2936, 2905, 2869, 1464, 1458, 1454, 1380, 1370, 1264, 1247, 1207, 1164, 1086, 1053, 1012, 880, 854 cm^{-1};
MS (EI, 70 eV) *m/z*: 296 ($M^{+\cdot}$, <1%), 281 [$(M-CH_3\cdot)^+$, 33], 69 (84), 55 (66), 43 (100), 41 (70);
HREIMS Found: $M^{+\cdot}$, 296.1994. Calculated for $C_{17}H_{28}O_4$ $M^{+\cdot}$, 296.1988.
Optical rotation $[\alpha]_D^{22}$ -18.0 (*c* 0.45, $CHCl_3$).

Concentration of fraction B afforded a 1:1.2 mixture of adduct **139a** and starting material **138a** (5 mg) as a clear, colourless oil. Spectral data of compound **138a** have been shown on page 108.

(3a*S*,4*S*,7*R*,7a*R*,9*S*)-9-[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3a,4,5,6,7,7a-hexahydro-2,2,7-trimethyl-4,7-ethano-1,3-benzodioxole (139b)



138b **139b**

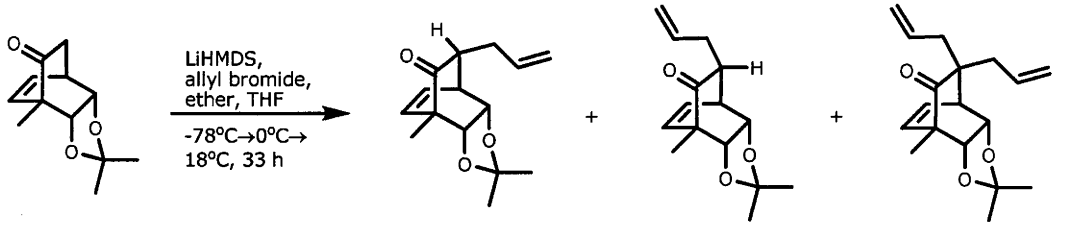
Adduct **138b** (19 mg, 0.06 mmol) was treated with Wilkinson's catalyst in the same way as described above for compound **138a**. After 21 h starting material remained so the reaction mixture was cooled to room temperature and a second portion of Wilkinson's catalyst (18 mg) and more *m*-xylene (2.20 ml) were added and the mixture was heated, once again, at 130°C and for 24 h. The reaction was again cooled to room temperature and worked up as described for **139a**. The resulting brown-black liquid that remained was diluted with a small amount of 1:4 v/v ethyl acetate/hexane and the resulting solution applied to the top of a flash chromatography column, elution of which (1:4 v/v ethyl acetate/hexane) afforded two fractions, A and B.

Concentration of fraction A (R_f = 0.5 in 1:4 v/v ethyl acetate/hexane) afforded adduct **139b** (7 mg, 39%) as a white, crystalline solid, m.p. 64-66°C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.12-4.04 (complex m, 3H), 3.75 (dd, J = 8.1 and 1.2 Hz, 1H), 3.64-3.61 (complex m, 1H), 2.12-2.10 (complex m, 1H), 1.80-1.73 (complex m, 1H), 1.68-1.56 (complex m, 2H), 1.50 (s, 3H), 1.49-1.43 (complex m, 1H), 1.38 (s, 3H), 1.35 (s, 3H), 1.35 (s, 3H), 1.35-1.25 (complex m, 1H), 0.92-0.85 (complex m, 1H), 0.84 (s, 3H), 0.75 (dd, J = 13.7 and 6.3 Hz, 1H);
^{13}C NMR (125 MHz, $CDCl_3$): δ 109.1 (C), 108.0 (C), 79.8 (CH), 77.6 (CH), 76.5 (CH), 68.4 (CH_2), 37.5 (CH), 33.8 (CH_2), 31.9 (C), 30.0 (CH), 27.1 (CH_3), 25.9 (CH_3), 25.7 (CH_3), 25.4 (CH_2), 24.6 (CH_3), 24.2 (CH_3), 14.1 (CH_2);
IR ν_{max} (KBr) 2986, 2935, 2877, 1469, 1454, 1379, 1370, 1261, 1207, 1166, 1137, 1103, 1072, 1029, 881, 856 cm^{-1};
MS (EI, 70 eV) *m/z*: 296 ($M^{+\cdot}$, <1%), 281 [$(M-CH_3\cdot)^+$, 100], 163 (25), 43 (49);
HREIMS Found: $(M-CH_3\cdot)^+$, 281.1756. Calculated for $C_{17}H_{28}O_4$ $(M-CH_3\cdot)^+$, 281.1753.
Optical rotation $[\alpha]_D^{20}$ +42.0 (*c* 0.1, $CHCl_3$).

Concentration of fraction B (R_f = 0.4 in 1:4 v/v ethyl acetate/hexane) afforded starting material **138b** (1 mg, 5%), which was identical, in all respects, with an authentic sample.

(3a*S*,4*S*,7*S*,7a*R*,9*S*)-9-Allyl-3a,4,7,7a-tetrahydro-2,2,7-trimethyl-4,7-ethano-1,3-benzodioxol-8-one (144a), (3a*S*,4*S*,7*S*,7a*R*,9*R*)-9-Allyl-3a,4,7,7a-tetrahydro-2,2,7-trimethyl-4,7-ethano-1,3-benzodioxol-8-one (144b) and (3a*S*,4*S*,7*S*,7a*R*)-9,9-Diallyl-3a,4,7,7a-tetrahydro-2,2,7-trimethyl-4,7-ethano-1,3-benzodioxol-8-one (145).



143 **144a** **144b** **145**

LiHMDS (1.44 ml of a 1 M solution in THF, 1.44 mmol, 2 eq) was cooled to -78°C and diluted with diethyl ether (6 ml). A solution of ketone **144** (150 mg, 0.72 mmol) in diethyl ether (1.2 ml) was then added dropwise and the reaction mixture stirred at -78°C for 2 h then warmed to 0°C. Allyl bromide (87 mg, 0.72 mmol, 1 eq) was added over 0.25 h. The reaction mixture was allowed to reach room temperature overnight. At this point TLC analysis showed that starting material was still present in the reaction mixture, so it was recooled to -78°C then LiHMDS (0.36 ml of a 1 M solution in THF, 0.36 mmol,0.5 eq) was added. The ensuing mixture was stirred for 1 h at -78°C then warmed to 0°C. Additional allyl bromide (44 mg, 0.36 mmol, 0.5 eq) was added over 0.17 h then the reaction mixture was allowed to warm to 18°C and after 14 h it was quenched with ammonium chloride (2 ml of a saturated aq. solution). The separated aqueous phase was extracted with diethyl ether (3 x 5 ml) and the combined organic phases were washed with brine (1 x 3 ml) before being dried (magnesium sulfate), filtered and concentrated under reduced pressure. Subjection of the resulting light yellow oil to column chromatography (silica, 1:9 v/v ethyl acetate/hexane) gave three fractions, A, B and C.

Concentration of fraction A (R_f = 0.4 in 1:9 v/v ethyl acetate/hexane) afforded compound **145** (29 mg, 14%) as a clear, colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.33 (dd, J = 7.6 and 6.6 Hz, 1H), 5.92-5.76 (complex m, 2H), 5.64 (dt, J = 7.6 and 1.4 Hz, 1H), 5.17-4.97 (complex m, 4H), 4.74 (dd, J = 7.1 and 3.6 Hz, 1H), 4.09 (dd, J = 7.1 and 1.4 Hz, 1H), 3.05 (ddd, J = 6.6, 3.6 and 1.4 Hz, 1H), 2.35-2.29 (complex m, 2H), 2.12 (dd, J = 14.5 and 8.5 Hz, 1H), 2.00 (dd, J = 14.5 and 7.8 Hz, 1H), 1.36 (s, 3H), 1.31 (s, 3H), 1.30 (s, 3H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 212.2 (C), 134.3 (CH), 134.0 (CH), 132.7 (CH), 129.6 (CH), 118.9 (CH_2), 117.9 (CH_2), 110.2 (C), 79.9 (CH), 76.0 (CH), 55.8 (C), 47.3 (C), 42.8 (CH), 41.7 (CH_2), 37.4 (CH_2), 25.3 (CH_3), 25.1 (CH_3), 14.6 (CH_3);
IR ν_{max} (KBr) 2978, 2935, 1718, 1638, 1450, 1380, 1372, 1265, 1209, 1166, 1073, 1065, 1049, 996, 969, 916, 880, 825, 731, 711, 512 cm^{-1};
MS (ESI, +ve ion mode) *m/z*: 311 [$(M+Na)^+$, 100%], 277 (45), 161 (41), 147 (47), 121 (37), 102 (49), 74 (43);
HRESMS Found: $(M+Na)^+$, 311.1625. Calculated for $C_{18}H_{24}O_3$ $(M+Na)^+$, 311.1623.
Optical rotation $[\alpha]_D^{17}$ +205.8 (*c* 1.25, $CHCl_3$).

Concentration of fraction B (R_f = 0.4 in 1:9 v/v ethyl acetate/hexane) afforded compound **144a** (13 mg, 7%) as a white, crystalline solid, m.p. 69-80°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.40 (ddd, *J* = 8.1, 6.5 and 0.7 Hz, 1H), 5.86-5.72 (complex m, 1H), 5.74 (dt, *J* = 8.1 and 1.5 Hz, 1H), 5.17-5.10 (complex m, 1H), 4.63 (dd, *J* = 7.1 and 3.3 Hz, 1H), 4.00 (dd, *J* = 7.1 and 1.4 Hz, 1H), 3.25-3.20 (complex m, 1H), 2.53 (dtt, *J* = 14.4, 5.1 and 1.5 Hz, 1H), 2.13 (ddd, *J* = 11.4, 5.1 and 3.0 Hz, 1H), 1.89 (ddd, *J* = 14.4, 11.4 and 8.5 Hz, 1H), 1.37 (s, 3H), 1.32 (s, 3H), 1.31 (s, 3H);
^{13}C NMR (75 MHz, $CDCl_3$): δ 212.2 (C), 135.2 (CH), 134.7 (CH), 131.6 (CH), 117.3 (CH_2), 110.4 (C), 80.0 (CH), 75.5 (CH), 55.0 (C), 44.5 (CH), 37.5 (CH), 32.9 (CH_2), 25.3 (CH_3), 25.0 (CH_3), 14.5 (CH_3);
IR ν_{max} (KBr) 3056, 2979, 2935, 2905, 2869, 1724, 1641, 1452, 1373, 1265, 1246, 1209, 1165, 1093, 1065, 995, 917, 887, 872, 725, 693 cm^{-1};
MS (EI, 70 eV) *m/z*: 248 ($M^{+\bullet}$, 7%), 233 [$(M-CH_3\bullet)^+$, 29], 190 (68), 161 (62), 145 (81), 121 (64), 108 (95), 100 (100);
HREIMS Found: $M^{+\bullet}$, 248.1418. Calculated for $C_{15}H_{20}O_3$ $M^{+\bullet}$, 248.1412.
Elemental analysis Found: C, 72.52; H, 8.22; $C_{15}H_{20}O_3$ requires: C, 72.55; H, 8.12%;
Optical rotation $[\alpha]_D^{17}$ +269.1 (*c* 1, $CHCl_3$).

Some of the material was recrystallised (hexane) and the colourless needles that were obtained submitted to X-ray analysis.

Concentration of fraction C (R_f = 0.3 in 1:9 v/v ethyl acetate/hexane) afforded compound **144b** (48 mg, 26%) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.24 (t, *J* = 7.1 Hz, 1H), 5.80-5.64 (complex m, 2H), 5.07-4.99 (complex m, 2H), 4.46 (ddd, *J* = 7.1, 3.4 and 0.8 Hz, 1H), 4.06 (dd, *J* =

7.1 and 1.4 Hz, 1H), 3.18-3.14 (complex m, 1H), 2.63-2.55 (complex m, 1H), 1.90-1.74 (complex m, 2H), 1.36 (s, 3H), 1.31 (s, 3H), 1.30 (s, 3H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 210.4 (C), 135.7 (CH), 132.6 (CH), 130.3 (CH), 117.0 (CH_2), 110.5 (C), 79.6 (CH), 79.2 (CH), 54.7 (C), 44.1 (CH), 38.8 (CH), 35.9 (CH_2), 25.3 (CH_3), 24.9 (CH_3), 14.5 (CH_3);

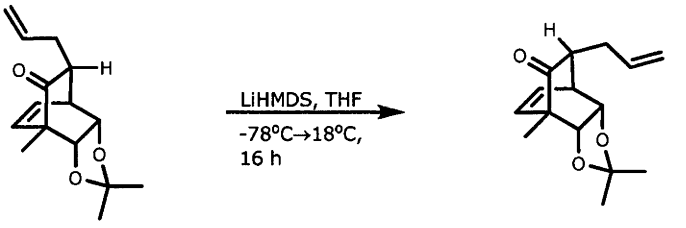
IR ν_{max} (KBr) 2978, 2935, 2889, 1722, 1641, 1452, 1374, 1262, 1251, 1208, 1163, 1142, 1095, 1079, 1064, 1047, 994, 970, 919, 887, 878, 840, 723, 690 cm^{-1};

MS (EI, 70 eV) *m/z*: 248 ($M^{+\bullet}$, 6%), 233 [$(M\text{-}CH_3\bullet)^+$, 24], 190 (65), 161 (100), 145 (71), 108 (82), 100 (80);

HREIMS Found: $M^{+\bullet}$, 248.1408. Calculated for $C_{15}H_{20}O_3$ $M^{+\bullet}$, 248.1412.

Optical rotation $[\alpha]_D^{18}$ +197.3 (*c* 1.65, $CHCl_3$).

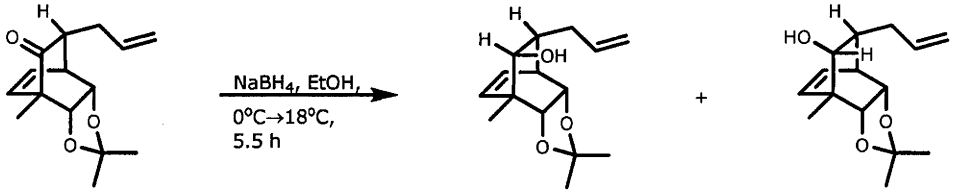
(3a*S*,4*S*,7*S*,7a*R*,9*S*)-9-Allyl-3a,4,7,7a-tetrahydro-2,2,7-trimethyl-4,7-ethano-1,3-benzodioxol-8-one (144a).



144b **144a**

A solution of ketone **144b** (222 mg, 0.89 mmol) in THF (0.89 ml) was cooled to -78°C then treated, dropwise, with LiHMDS (0.89 ml of a 1 M solution in THF, 0.89 mmol, 1 eq). The ensuing mixture was stirred at -78°C for 0.08 h and then allowed to slowly warm to 18°C. After 16 h at this temperature the reaction mixture was quenched with distilled water (2 ml). The separated aqueous layer was extracted with diethyl ether (3 x 4 ml) and the combined organic phases were washed with brine (1 x 4 ml) then dried (magnesium sulfate), filtered and concentrated under reduced pressure to give 187 mg of a light-yellow oil. ^{1}H NMR analysis of this material established that it was composed of a 1:3.6 mixture of ketones **144a** and **144b**.

(3a*S*,4*S*,7*R*,7a*R*,8*S*,9*S*)-9-Allyl-8-hydroxy-3a,4,7,7a-tetrahydro-2,2,7-trimethyl-4,7-ethano-1,3-benzodioxole (146a) and (3a*S*,4*S*,7*R*,7a*R*,8*R*,9*S*)-9-Allyl-8-hydroxy-3a,4,7,7a-tetrahydro-2,2,7-trimethyl-4,7-ethano-1,3-benzodioxole (146b).



144a **146a** **146b**

A solution of ketone **144a** (36 mg, 145 μmol) in ethanol (5 ml) was cooled to 0°C then sodium borohydride (19 mg, 502 μmol, 3.5 eq.) was added in one portion. The resulting mixture was allowed to warm to 18°C. After 4 h an additional amount of sodium borohydride (5 mg) was added and the reaction stirred at 18°C for another 1.5 h. The reaction mixture was then quenched with ammonium chloride (10 ml of a saturated aq. solution). After 0.08 h the thick, white aqueous phase was diluted with distilled water and extracted with ethyl acetate (3 x 20 ml). The combined organic extracts were washed with brine (1 x 20 ml) then dried (magnesium sulfate), filtered and concentrated under reduced pressure to yield a clear, colourless oil. Subjection of this material to column chromatography (silica, 1:4 v/v ethyl acetate/hexane) gave two fractions, A and B.

Concentration of fraction A (R_f = 0.4 in 1:4 v/v ethyl acetate/hexane) afforded alcohol **146a** (9 mg, 25%) as a white, crystalline solid, m.p. 96-99°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.18 (ddd, J = 8.2, 6.3 and 0.8 Hz, 1H), 5.95-5.82 (complex m, 1H), 5.66 (dt, J = 8.2 and 1.2 Hz, 1H), 5.18-5.04 (complex m, 2H), 4.47 (ddd, J = 7.3, 3.0 and 0.5 Hz, 1H), 4.38 (dd, J = 7.3 and 1.0 Hz, 1H), 3.64 (dd, J = 9.1 and 3.3 Hz, 1H), 2.77-2.72 (complex m, 1H), 2.46-2.34 (complex m, 1H), 2.15-2.04 (complex m, 1H), 1.97-1.87 (complex m, 1H), 1.68 (d, J = 3.3 Hz, 1H), 1.39 (s, 3H), 1.32 (s, 3H), 1.28 (s, 3H);
^{13}C NMR (75 MHz, $CDCl_3$): δ 138.7 (CH), 134.0 (CH), 134.0 (CH), 115.8 (CH_2), 107.4 (C), 78.0 (CH), 75.1 (CH), 72.3 (CH), 43.9 (C), 39.6 (CH), 38.7 (CH), 32.5 (CH_2), 25.4 (CH_3), 24.9 (CH_3), 18.8 (CH_3);
IR ν_{max} (KBr) 3486, 3073, 3047, 2977, 2961, 2933, 2909, 2875, 1640, 1458, 1380, 1371, 1267, 1251, 1207, 1165, 1144, 1052, 1011, 998, 965, 913, 886, 731, 704, 667, 519 cm^{-1};
MS (EI, 70 eV) *m/z*: 250 ($M^{+\bullet}$, 1%), 235 [$(M-CH_3\bullet)^+$, 29], 109 (100), 108 (77), 105 (95), 100 (48), 57 (43), 55 (44), 43 (78), 41 (51);

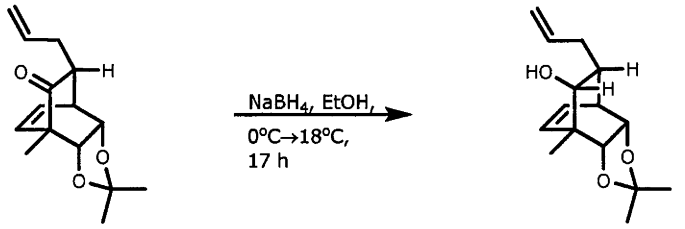
HREIMS Found: $M^{+\bullet}$, 250.1571. Calculated for $C_{15}H_{22}O_3$ $M^{+\bullet}$, 250.1569.

Optical rotation $[\alpha]_D^{21}$ -27.8 (*c* 0.55, $CHCl_3$).

Concentration of fraction B (R_f = 0.2 in 1:4 v/v ethyl acetate/hexane) afforded alcohol **146b** (14 mg, 39%) as a white, crystalline solid, m.p. 61-64°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.30 (ddd, *J* = 8.2, 6.5 and 1.0 Hz, 1H), 5.89-5.76 (complex m, 1H), 5.69 (dq, *J* = 8.2 and 1.2 Hz, 1H), 5.15-5.04 (complex m, 2H), 4.38 (dd, *J* = 7.3 and 2.9 Hz, 1H), 3.82 (dd, *J* = 7.3 and 1.2 Hz, 1H), 3.01 (broad dd, *J* = 7.6 and 3.6 Hz, 1H), 2.79-2.74 (complex m, 1H), 2.33-2.23 (complex m, 1H), 2.16-2.05 (complex m, 1H), 1.44-1.35 (complex m, 1H), 1.33 (s, 6H), 1.28 (s, 3H), 1.25 (d, *J* = 7.6 Hz, 1H);
^{13}C NMR (75 MHz, $CDCl_3$): δ 136.5 (CH), 133.7 (CH), 132.1 (CH), 116.5 (CH_2), 109.2 (C), 81.1 (CH), 77.7 (CH), 75.3 (CH), 47.7 (CH), 45.1 (C), 37.4 (CH), 36.8 (CH_2), 25.4 (CH_3), 24.9 (CH_3), 17.8 (CH_3);
IR ν_{max} (KBr) 3463, 3048, 2977, 2931, 2905, 2870, 1641, 1458, 1443, 1380, 1372, 1269, 1257, 1207, 1166, 1142, 1077, 1060, 1026, 998, 914, 881, 809, 736, 511 cm^{-1};
MS (EI, 70 eV) *m/z*: 250 ($M^{+\bullet}$, <1%), 235 [$(M-CH_3^{\bullet})^+$, 29], 133 (78), 117 (80), 109 (100), 108 (65), 105 (90), 43 (73), 41 (64);
HREIMS Found: $M^{+\bullet}$, 250.1571. Calculated for $C_{15}H_{22}O_3$ $M^{+\bullet}$, 250.1569.
Elemental analysis Found: C, 72.08; H, 8.56; $C_{15}H_{22}O_3$ requires: C, 71.97; H, 8.86%;
Optical rotation $[\alpha]_D^{21}$ +8.4 (*c* 0.9, $CHCl_3$).

(3aS,4S,7R,7aR,8R,9R)-9-Allyl-8-hydroxy-3a,4,7,7a-tetrahydro-2,2,4-trimethyl-4,7-ethano-1,3-benzodioxole (146c).



144b **146c**

A solution of ketone **144b** (100 mg, 403 μmol) in ethanol (19 ml) was cooled to 0°C then sodium borohydride (52 mg, 1.37 mmol, 3.4 eq.) was added in one portion. The reaction mixture was allowed to slowly warm to 18°C. After 17 h it was quenched with ammonium chloride (10 ml of a saturated aq. solution), stirred for 0.17 h and diluted with distilled water to dissolve a white precipitate that had formed. The solvent was then evaporated under reduced pressure and the remaining material extracted with ethyl acetate (3 x 20 ml). The combined organic phases were washed with brine (1 x 10 ml) then dried (magnesium sulfate), filtered and concentrated under reduced pressure. The resulting colourless oil was subjected to column chromatography (silica, 1:4 v/v ethyl acetate/hexane) and concentration of the appropriate fractions then gave alcohol **146c** (61 mg, 61%) as a white, crystalline solid, m.p. 94.6-94.9°C.

R_f = 0.3 in 1:4 v/v ethyl acetate/hexane;

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.17 (dd, J = 8.2 and 6.6 Hz, 1H), 5.90-5.82 (complex m, 1H), 5.76-5.74 (complex m, 1H), 5.09-5.02 (complex m, 2H), 4.18 (dd, J = 7.1 and 3.4 Hz, 1H), 3.85 (dd, J = 7.1 and 1.0 Hz, 1H), 3.55 (t, J = 8.2 Hz, 1H), 2.81-2.79 (complex m, 1H), 2.34-2.28 (complex m, 1H), 1.88-1.82 (complex m, 1H), 1.74-1.79 (q, J = 8.2 Hz, 1H), 1.37 (s, 3H), 1.32 (s, 3H), 1.27 (s, 3H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 138.2 (CH), 133.3 (CH), 131.4 (CH), 116.0 (CH_2), 109.1 (C), 80.7 (CH), 79.3 (CH), 73.0 (CH), 45.3 (C), 40.5 (CH), 38.5 (CH), 33.7 (CH_2), 25.4 (CH_3), 24.9 (CH_3), 18.5 (CH_3);

IR ν_{max} (KBr) 3490, 2978, 2965, 2909, 2878, 1456, 1402, 1385, 1260, 1211, 1201, 1143, 1079, 1054, 1043, 1011, 994, 908, 883, 837, 809, 720 cm^{-1};

MS (EI, 70 eV) *m/z*: 250 ($M^{+\cdot}$, 3%), 235 [$(M-CH_3\cdot)^+$, 69], 109 (98), 108 (100), 105 (94), 100 (80), 43 (71);

HREIMS Found: $M^{+\cdot}$, 250.1561. Calculated for $C_{15}H_{22}O_3$ $M^{+\cdot}$, 250.1569.

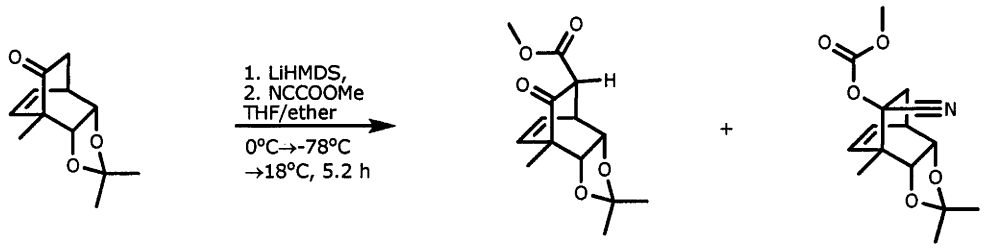
Elemental analysis Found: C, 71.72; H, 8.63; $C_{15}H_{22}O_3$ requires: C, 71.97; H,

8.86%;

Optical rotation $[\alpha]_D^{20}$ +32.9 (*c* 0.7, $CHCl_3$).

Some of the material was recrystallised (hexane) and the colourless needles that were obtained submitted to X-ray analysis.

(3a*S*,4*S*,7*S*,7a*R*,9*R*)-Methyl 8-oxo-3a,4,7,7a-tetrahydro-2,2,7-trimethyl-4,7-ethano-1,3-benzodioxol-9-carboxylate (151) and (3a*S*,4*R*,7*S*,7a*R*,8*R*)-Methyl 8-cyano-3a,4,7,7a-tetrahydro-2,2,7-trimethyl-4,7-ethano-1,3-benzodioxol-8-carbonate (152b).



143 **151** **152b**

A solution of ketone **143** (100 mg, 0.48 mmol) in freshly distilled diethyl ether (0.67 ml) was cooled to 0°C then treated, dropwise, with LiHMDS (0.72 ml of a 1 M solution in THF, 0.72 mmol, 1.5 eq). The resulting mixture was stirred at 0°C for 3 h, then cooled to -78°C, diluted with diethyl ether (1.35 ml) and treated, dropwise, with methyl cyanoformate (0.38 ml, 4.80 mmol, 10 eq). The resulting mixture was stirred at -78°C for 0.33 h and then allowed to slowly warm to room temperature. After 1.83 h the reaction mixture was quenched with distilled water (5 ml). The layers were separated and the aqueous phase extracted with diethyl ether (5 x 2.5 ml). The combined organic layers were then washed with brine (1 x 10 ml) before being dried (magnesium sulfate), filtered and concentrated under reduced pressure. The resulting dark orange oil was subjected to column chromatography (silica, 1:4 v/v ethyl acetate/hexane) to afford two fractions, A and B.

Concentration of fraction A (R_f = 0.3 in 1:4 v/v ethyl acetate/hexane) afforded compound **152b** (19 mg, 13%) as a white, crystalline solid, m.p. 135-136°C. A sample of this material was recrystallised (hexane/benzene) to give white needles that were used for an X-ray analysis and the collection of data shown below.

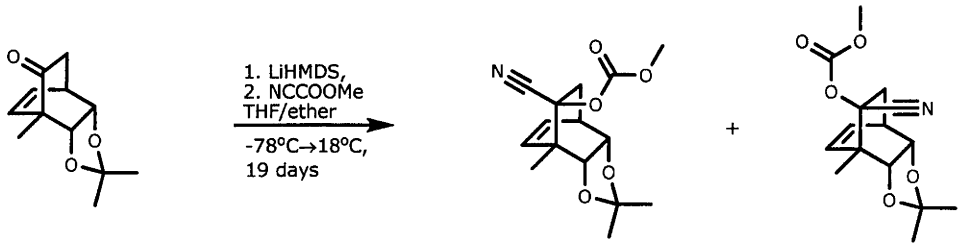
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.24 (dd, J = 8.1 and 6.7 Hz, 1H), 5.72 (d, J = 8.1 Hz, 1H), 4.34-4.33 (complex m, 2H), 3.81 (s, 3H), 2.95-2.92 (complex m, 1H), 2.42 (dd, J = 15.7 and 2.1 Hz, 1H), 1.94 (dd, J 15.7 and 3.7 Hz, 1H), 1.54 (s, 3H), 1.32 (s, 3H), 1.30 (s, 3H);
^{13}C NMR (75 MHz, $CDCl_3$): δ 153.4 (C), 131.9 (CH), 131.4 (CH), 117.6 (C), 109.9 (C), 78.4 (CH), 77.6 (CH), 76.8 (C), 55.4 (CH_3), 45.8 (C), 38.9 (CH_2), 33.9 (CH), 25.3 (CH_3), 25.0 (CH_3), 16.3 (CH_3);
IR ν_{max} (KBr) 2987, 2940, 2901, 1758, 1444, 1379, 1287, 1274, 1246, 1225, 1207, 1078, 996 cm^{-1};
MS (EI, 70 eV) *m/z*: 293 ($M^{+\cdot}$, 7%), 278 [$(M-CH_3\cdot)^+$, 71], 159 (100), 130 (75), 123 (69), 59 (69), 43 (84);

HREIMS Found: $M^{+\cdot}$, 293.1264. Calculated for $C_{15}H_{19}NO_5$ $M^{+\cdot}$, 293.1263.
Elemental analysis Found: C, 61.17; H, 6.24; N, 4.63; $C_{15}H_{19}NO_5$ requires: C, 61.42; H, 6.53; N, 4.78%;
Optical rotation $[\alpha]_D^{21}$ +87.3 (*c* 1, $CHCl_3$).

Concentration of fraction B (R_f = 0.2 in 1:4 v/v ethyl acetate/hexane) afforded a 6.7:1 mixture of *β*-ketoester **151** and its epimer (46 mg, 35%) as determined by ^{1}H NMR analysis. The amount of *epi*-**151** was very small and this compound was not isolated as such. Some subfractions of B that contained adduct **151** purely were separately combined to give a white solid that was recrystallised (ethyl acetate/hexane). The thus obtained colourless crystals, m.p. 115-116°C, were analysed as shown below.

^{1}H NMR (300 MHz, $CDCl_3$): *δ* 6.44 (broad dd, *J* = 8.1 and 6.4 Hz, 1H), 5.71 (broad dt, *J* = 8.1 and 1.5 Hz, 1H), 4.49 (broad dd, *J* = 7.1 and 3.4 Hz, 1H), 4.08 (dd, *J* = 7.1 and 1.5 Hz, 1H), 3.71 (s, 3H), 3.46-3.41 (complex m, 1H), 2.92 (d, *J* 1.6 Hz, 1H), 1.37 (s, 3H), 1.35 (s, 3H), 1.30 (s, 3H);
^{13}C NMR (150 MHz, $CDCl_3$): *δ* 202.0 (C), 167.8 (C), 133.0 (CH), 129.2 (CH), 110.9 (C), 79.4 (CH), 78.1 (CH), 54.6 (C), 52.8 (CH_3), 50.4 (CH), 38.3 (CH), 25.3 (CH_3), 25.0 (CH_3), 14.6 (CH_3);
IR ν_{max} (KBr) 2979, 2949, 2937, 2891, 1747, 1725, 1374, 1262, 1243, 1207, 1163, 1088, 1063, 1034, 973, 714 cm^{-1};
MS (EI, 70 eV) *m/z*: 266 ($M^{+\cdot}$, 48%), 251 [$(M-CH_3\cdot)^+$, 45], 235 [$(M-CH_3O\cdot)^+$, 24], 176 (100), 148 (93), 121 (71), 108 (69), 100 (89), 91 (63), 85 (65), 43 (68);
HREIMS Found: $M^{+\cdot}$, 266.1163. Calculated for $C_{14}H_{18}O_5$ $M^{+\cdot}$, 266.1154;
Elemental analysis Found: C, 63.43; H, 6.91; $C_{14}H_{18}O_5$ requires: C, 63.15; H, 6.81;
Optical rotation $[\alpha]_D^{19}$ +210.0 (*c* 1, $CHCl_3$).

(3a*S*,4*R*,7*S*,7a*R*,8*S*)-Methyl 8-cyano-3a,4,7,7a-tetrahydro-2,2,7-trimethyl-4,7-ethano-1,3-benzodioxol-8-carbonate (152a) and (3a*S*,4*R*,7*S*,7a*R*,8*R*)-Methyl 8-cyano-3a,4,7,7a-tetrahydro-2,2,7-trimethyl-4,7-ethano-1,3-benzodioxol-8-carbonate (152b).



143 **152a** **152b**

LiHMDS (3.60 ml of a 1 M solution in THF, 3.60 mmol, 1.5 eq) was cooled to -78°C then a solution of ketone **143** (500 mg, 2.40 mmol) in diethyl ether (24 ml) was added dropwise and the ensuing mixture stirred for 2.25 h at -78°C. Methyl cyanoformate (0.21 ml, 2.64 mmol, 1.1 eq) was then added dropwise over 0.5 h and stirring continued at this temperature for 3 h. After this time TLC analysis show that starting material still was present and the reaction was allowed to warm to room temperature and left to stand for 19 days. Before discarding the mixture it was analysed once more by TLC, which showed a significant amount of an unknown species. The solution was therefore quenched with distilled water (100 ml). The separated aqueous phase was extracted with dichloromethane (5 x 50 ml) then the combined organic layers were washed with brine (1 x 100 ml) before being dried (magnesium sulfate), filtered and concentrated under reduced pressure. The obtained yellow oil was subjected to column chromatography (silica, 1:4 v/v ethyl acetate/hexane) to afford two fraction, A and B.

Concentration of fraction A (R_f = 0.3 in 1:4 v/v ethyl acetate/hexane) gave compound **152b** (335 mg, 48%) as a white, crystalline solid. This material was identical, in all respects, with an authentic sample.

Concentration of fraction B (R_f = 0.2 in 1:4 v/v ethyl acetate/hexane) gave compound **152a** (156 mg, 22%) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.30 (dd, J = 8.2 and 6.5 Hz, 1H), 5.82 (dd, J = 8.2 and 1.1 Hz, 1H), 4.33-4.26 (complex m, 2H), 3.85 (s, 3H), 3.01-2.94 (complex m, 1H), 2.59 (dd, J = 15.2 and 4.3 Hz, 1H), 1.69 (dd, J = 15.2 and 1.8 Hz, 1H), 1.57 (s, 3H), 1.31 (s, 3H), 1.27 (s, 3H);
^{13}C NMR (75 MHz, $CDCl_3$): δ 153.6 (C), 133.5 (CH), 132.5 (CH), 117.9 (C), 109.0 (C), 77.9 (CH), 77.5 (C), 77.0 (CH), 55.5 (CH_3), 45.6 (C), 37.4 (CH_2), 34.3 (CH), 25.3 (CH_3), 24.9 (CH_3), 16.2 (CH_3);

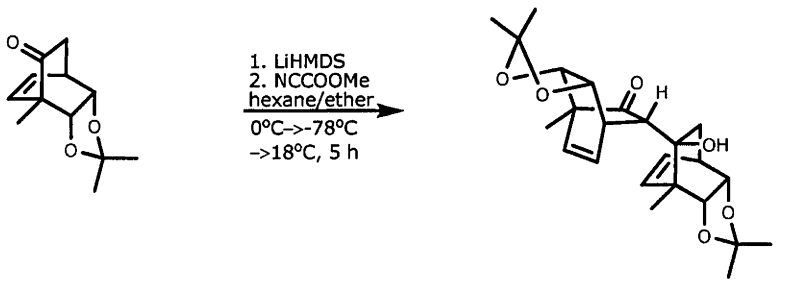
IR ν_{max} (KBr) 2980, 2939, 2242 (weak), 1762, 1443, 1376, 1277, 1259, 1235, 1208, 1166, 1109, 1083, 1062, 1026, 995, 941, 893, 872, 823, 788, 756, 732 cm^{-1};

MS (EI, 70 eV) *m/z*: 278 [$(M\text{-}CH_3\cdot)^+$, 51%], 159 (100), 130 (68), 108 (53), 100 (48), 59 (45), 43 (59);

HREIMS Found: $(M\text{-}CH_3\cdot)^+$, 278.1028. Calculated for $C_{15}H_{19}NO_5$ $(M\text{-}CH_3\cdot)^+$, 278.1028.

Optical rotation $[\alpha]_D^{20}$ +88.7 (*c* 1.05, $CHCl_3$).

(3a*S*,4*S*,7*S*,7a*R*,9*S*)-9-[(3a*S*,4*R*,7*S*,7a*R*,8*R*)-8-Hydroxy-3a,4,7,7a-tetrahydro-2,2,7-trimethyl-4,7-ethano-1,3-benzodioxol-8-yl]-3a,4,7,7a-tetrahydro-2,2,7-trimethyl-4,7-ethano-1,3-benzodioxol-8-one (153).



143 **153**

A solution of ketone **143** (100 mg, 0.48 mmol) in diethyl ether (0.67 ml) was cooled to 0°C then treated, dropwise, with LiHMDS (0.72 ml of a 1 M solution in hexane, 0.72 mmol, 1.5 eq). The ensuing mixture was stirred at 0°C for 2.66 h, then cooled to -78°C and diluted with diethyl ether (1.35 ml). Methyl cyanoformate (0.38 ml, 4.80 mmol, 10 eq) was then added dropwise and the resulting mixture stirred at 0°C for 0.67 h then allowed to slowly warm to 18°C. After 1.5 h at this temperature the reaction was quenched with distilled water (5 ml). The layers were separated and the aqueous phase extracted with diethyl ether (5 x 2.5 ml). The combined organic layers were washed with brine (1 x 10 ml) then dried (magnesium sulfate), filtered and concentrated under reduced pressure. The yellow oil thus obtained was subjected to column chromatography (silica, 1:4 v/v ethyl acetate/hexane) and concentration of the appropriate fractions then gave adduct **153** (44 mg, 46%) as a white, crystalline solid, no m.p. – sublimes on heating.

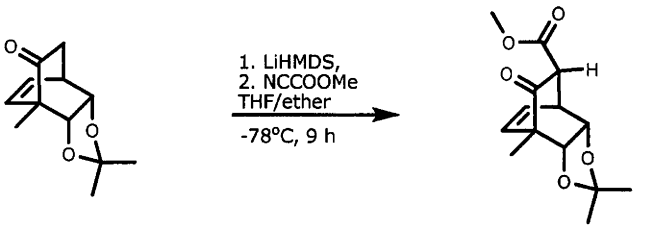
R_f = 0.4 in 1:4 v/v ethyl acetate/hexane;
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.13-6.06 (complex m, 2H), 5.75 (broad d, J = 8.0 Hz, 1H), 5.58 (broad d, J = 8.0 Hz, 1H), 4.74 (broad s, 1H), 4.55 (dd, J = 7.0 and 0.8 Hz, 1H), 4.49 (dd, J = 7.0 and 3.3 Hz, 1H), 4.35 (dd, J = 7.0 and 2.2 Hz, 1H), 4.10 (dd, J = 7.0 and 1.2 Hz, 1H), 3.21-3.18 (complex m, 1H), 2.76-2.73 (complex m, 1H), 2.13 (s, 1H), 1.67 (dd, J = 14.0 and 3.4 Hz, 1H), 1.38 (dd, J 14.0 and 2.6 Hz, 1H), 1.35 (s, 3H), 1.34 (s, 3H), 1.31 (s, 6H), 1.29 (s, 3H), 1.26 (s, 3H);
^{13}C NMR (75 MHz, $CDCl_3$): δ 214.4 (C), 134.7 (CH), 133.7 (CH), 130.8 (CH), 129.0 (CH), 110.8 (C), 108.0 (C), 79.6 (CH), 79.5 (CH), 79.3 (CH), 78.9 (C), 78.1 (CH), 55.1 (C), 51.2 (CH), 45.5 (C), 37.6 (CH), 37.3 (CH_2), 35.8 (CH), 25.5 (CH_3), 25.2 (CH_3), 25.0 (CH_3), 25.0 (CH_3), 15.5 (CH_3), 14.2 (CH_3);
IR ν_{max} (KBr) 3483, 2977, 2938, 2883, 1702, 1371, 1256, 1206, 1163, 1075, 1054, 1028, 892, 878, 727 cm^{-1};
MS (EI, 70 eV) *m/z*: 401 [$(M\text{-}CH_3\cdot)^+$, 8%], 150 (49), 121 (57), 108 (100), 105 (66), 100 (94), 43 (58);

HREIMS Found: $(M\text{-}CH_3\cdot)^+$, 401.1964. Calculated for $C_{24}H_{32}O_6$ $(M\text{-}CH_3\cdot)^+$, 401.1964.

Optical rotation $[\alpha]_D^{19}$ +146.0 (*c* 0.5, $CHCl_3$).

A sample was recrystallised (hexane) to give colourless crystals that were subjected to X-ray analysis.

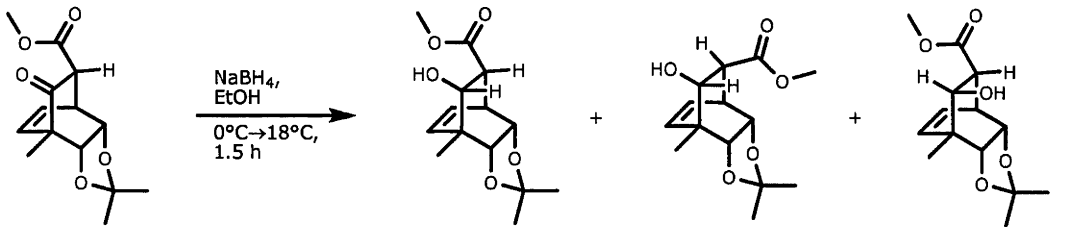
(3a*S*,4*S*,7*S*,7a*R*,9*R*)-Methyl 8-oxo-3a,4,7,7a-tetrahydro-2,2,7-trimethyl-4,7-ethano-1,3-benzodioxol-9-carboxylate (151).



143 **151**

LiHMDS (28.80 ml of a 1 M solution in THF, 28.80 mmol, 2 eq) was diluted with diethyl ether (132 ml) and cooled to -78°C. A solution of ketone **143** (3.00 g, 14.40 mmol) in diethyl ether (12 ml) was then added *via* syringe pump at the rate of 15 ml/h. After addition was complete, the resulting mixture was stirred at -78°C for 2.5 h then methyl cyanoformate (2.30 ml, 28.80 mmol, 2 eq) was added *via* syringe pump at 0.45 ml/h. The ensuing mixture was stirred at -78°C for 0.5 h after which it was poured into a 1:1 mixture of dichloromethane and distilled water (300 ml). The separated aqueous phase was extracted with dichloromethane (3 x 100 ml) and the combined organic layers were washed with brine (1 x 150 ml) then dried (magnesium sulfate), filtered and concentrated under reduced pressure. The orange oil thus obtained was subjected to column chromatography (silica, 1:4 v/v ethyl acetate/hexane) and concentration of the appropriate fractions (R_f = 0.2 in 1:4 v/v ethyl acetate/hexane) gave β-ketoester **151** (2.56 g, 67%) as a white, crystalline solid. This material was identical, in all respects, with an authentic sample.

(3a*S*,4*S*,7*R*,7a*R*,8*R*,9*R*)-Methyl 8-hydroxy-3a,4,7,7a-tetrahydro-2,2,7-trimethyl-4,7-ethano-1,3-benzodioxol-9-carboxylate (154a), (3a*S*,4*S*,7*R*,7a*R*,8*R*,9*S*)-Methyl 8-hydroxy-3a,4,7,7a-tetrahydro-2,2,7-trimethyl-4,7-ethano-1,3-benzodioxol-9-carboxylate (154b) and (3a*S*,4*S*,7*R*,7a*R*,8*S*,9*R*)-Methyl 8-hydroxy-3a,4,7,7a-tetrahydro-2,2,7-trimethyl-4,7-ethano-1,3-benzodioxol-9-carboxylate (154c).



151 **154a** **154b** **154c**

A solution of *β*-ketoester **151** (101 mg, 380 μmol) in ethanol (17.4 ml) was cooled to 0°C then treated, in one portion, with sodium borohydride (14.4 mg, 380 μmol, 1 eq). The reaction mixture was stirred at 0°C for 0.5 h then allowed to warm to 18°C. After 1 h at this temperature the reaction was quenched with ammonium chloride (5 ml of a saturated aq. solution) and, after a further 0.08 h, diluted with distilled water then concentrated under reduced pressure to *ca.* 1/3 of its original volume. The residue so obtained was mixed with dichloromethane (10 ml). The separated aqueous phase was extracted with dichloromethane (3 x 10 ml) and the combined organic phases were washed with brine (1 x 10 ml) before being dried (magnesium sulfate), filtered and concentrated under reduced pressure. The resulting yellow oil was subjected to column chromatography (silica, 1:7:12 v/v/v MeOH/ethyl acetate/hexane) to afford two fractions, A and B.

Concentration of fraction A (R_f = 0.4 in 1:7:12 v/v/v MeOH/ethyl acetate/hexane) yielded an inseparable 1.7:1 mixture of *trans* *β*-hydroxyesters **154b** and **154c** (25 mg, 24%) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): *δ* (compound **154b**) spectrum identical with that derived from a pure sample (see below);
^{1}H NMR (300 MHz, $CDCl_3$): *δ* (compound **154c**) 6.03 (dd, *J* = 8.1 and 6.0 Hz, 1H), 5.78-5.70 (complex m, 1H), 4.40 (ddd, *J* = 7.3, 3.2 and 0.8 Hz, 1H), 4.35 (dd, *J* = 7.3 and 0.8 Hz, 1H), 3.79 (broad d, *J* = 4.4 Hz, 1H), 3.69 (s, 3H), 3.22-3.14 (complex m, 1H), 2.28 (dd, *J* = 4.4 and 1.8 Hz, 1H), 1.36 (s, 3H), 1.32 (s, 3H), 1.28 (s, 3H) (signal due to OH proton obscured or overlapping);
^{13}C NMR (75 MHz, $CDCl_3$): *δ* (compound **154b**) spectrum identical with that derived from a pure sample (see below);

^{13}C NMR (75 MHz, $CDCl_3$): δ (compound **154c**) 173.7 (C), 134.9 (CH), 129.7 (CH), 108.5 (C), 78.6 (CH), 77.7 (CH), 75.0 (CH), 52.3 (CH_3), 49.9 (CH), 43.9 (C), 37.5 (CH), 25.4 (CH_3), 24.9 (CH_3), 17.7 (CH_3);

MS (EI, 70 eV) *m/z*: 268 ($M^{+\bullet}$, 2%), 253 [$(M\text{-}CH_3\bullet)^+$, 54], 133 (100), 109 (73), 108 (91), 105 (90), 100 (86), 43 (85);

HREIMS Found: $M^{+\bullet}$, 268.1306. Calculated for $C_{14}H_{20}O_5$ $M^{+\bullet}$, 268.1311.

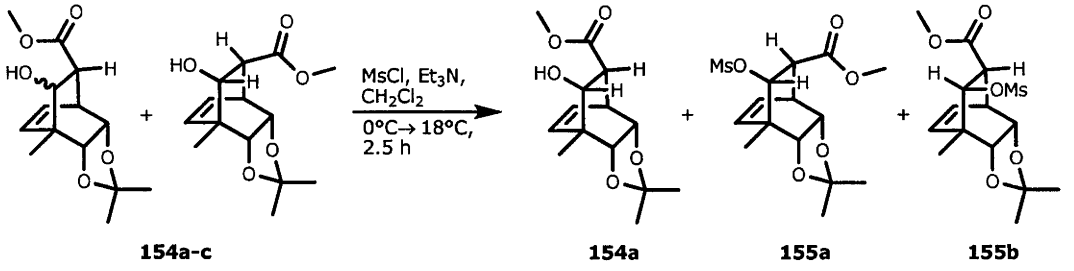
Concentration of fraction B (R_f = 0.4 in 1:7:12 v/v/v MeOH/ethyl acetate/hexane) gave *cis* β-hydroxyester **154a** (56 mg, 58%) as a white, crystalline solid, m.p. 84-86°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.35-6.29 (m, 1H), 5.74 (dd, J = 8.2 and 1.2 Hz, 1H), 4.17 (dd, J = 7.2 and 3.6 Hz, 1H), 3.83 (dd, J = 7.2 and 1.2 Hz, 1H), 3.72 (d, J = 8.6 Hz, 1H), 3.67 (s, 3H), 3.11-3.06 (complex m, 1H), 2.75 (d, J = 8.6 Hz, 1H), 2.10 (broad s, 1H), 1.37 (s, 3H), 1.31 (s, 3H), 1.26 (s, 3H);
^{13}C NMR (75 MHz, $CDCl_3$): δ 172.0 (C), 131.9 (CH), 131.5 (CH), 109.6 (C), 80.3 (CH), 78.3 (CH), 71.8 (CH), 51.9 (CH_3), 47.8 (CH), 44.9 (C), 36.2 (CH), 25.3 (CH_3), 24.9 (CH_3), 18.2 (CH_3);
IR ν_{max} (KBr) 3481, 2977, 2934, 2876, 1737, 1454, 1437, 1371, 1346, 1260, 1203, 1171, 1080, 1056, 1031, 883, 836, 731 cm^{-1};

MS (EI, 70 eV) *m/z*: 268 ($M^{+\bullet}$, <1%), 253 [$(M\text{-}CH_3\bullet)^+$, 26], 133 (63), 109 (61), 108 (100), 105 (47), 80 (43), 43 (40);
HREIMS Found: $(M\text{-}CH_3\bullet)^+$, 253.1076. Calculated for $C_{14}H_{20}O_5$ $(M\text{-}CH_3\bullet)^+$, 253.1076.

Optical rotation $[\alpha]_D^{18}$ +26.5 (*c* 0.9, $CHCl_3$).

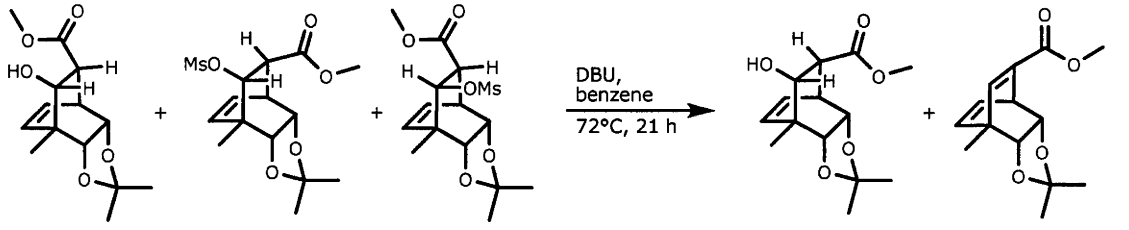
(3a*S*,4*S*,7*R*,7a*R*,8*R*,9*S*)-Methyl 8-methanesulfonyl-3a,4,7,7a-tetrahydro-2,2,7-trimethyl-4,7-ethano-1,3-benzodioxol-9-carboxylate (155a) and (3a*S*,4*S*,7*R*,7a*R*,8*S*,9*R*)-Methyl 8-methanesulfonyl-3a,4,7,7a-tetrahydro-2,2,7-trimethyl-4,7-ethano-1,3-benzodioxol-9-carboxylate (155b).



154a-c **154a** **155a** **155b**

Triethylamine (0.59 ml, 4.23 mmol, 1.5 eq) was added to a solution of a mixture of *β*-hydroxyesters **154a** and **154b-c** (2:1, 736 mg, 2.82 mmol) in dichloromethane (14 ml) and the resulting mixture cooled to 0°C then treated, dropwise, with mesyl chloride (0.24 ml, 3.10 mmol, 1.1 eq). The resulting reaction mixture was stirred at 0°C for 1 h and then at 18°C for 1.5 h before being diluted with dichloromethane (58 ml) and washed with ice water (1 x 70 ml), hydrochloric acid (1 x 70 ml of a 2 M aq. solution), sodium hydrogen carbonate (2 x 70 ml of a saturated aq. solution) and brine (1 x 70 ml). The organic phase was dried (magnesium sulfate), filtered and concentrated under reduced pressure to yield a 2:1.3:1 mixture of *cis*-alcohol **154a** and mesylates **155a** and **155b** (714 mg) as determined by ^{1}H NMR analysis. The light-yellow oil was used directly in the next step.

(3a*S*,4*S*,7*R*,7a*R*,8*R*,9*S*)-Methyl 8-hydroxy-3a,4,7,7a-tetrahydro-2,2,7-trimethyl-4,7-ethano-1,3-benzodioxol-9-carboxylate (154b) and (3a*S*,4*S*,7*R*,7a*R*)-Methyl 3a,4,7,7a-tetrahydro-2,2,7-trimethyl-4,7-etheno-1,3-benzodioxol-9-carboxylate (156).



154a **155a** **155b** **154b** **156**

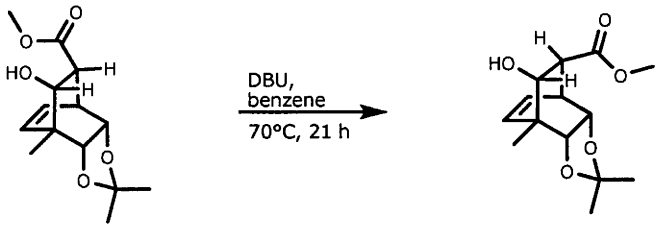
DBU (0.80 ml) was added to a solution of a crude 2:1.3:1 mixture of **154a**, **155a** and **155b** (714 mg) in benzene (10 ml) and the resulting mixture heated to 72°C for 21 h then cooled to 18°C and diluted with dichloro-methane (10 ml). The resulting solution was washed with hydrochloric acid (2 x 10 ml of a 2 M aq. solution), sodium hydrogen carbonate (1 x 10 ml of a saturated aq. solution) and brine (1 x 10 ml) then dried (magnesium sulfate), filtered and concentrated under reduced pressure. The yellow oil (356 mg) thus obtained was subjected to column chromatography (silica, 1:1 v/v ethyl acetate/hexane) to afford two fractions, A and B.

Concentration of fraction A (R_f = 0.8 in 1:7:12 v/v/v MeOH/ethyl acetate/hexane) afforded α,β-unsaturated ester **156** (177 mg, 25% over two steps) as a light-yellow oil.

***R*$_f$** = 0.6 in 1:4 v/v ethyl acetate/hexane;
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.92 (s, 1H), 6.34-6.28 (complex m, 1H), 5.99-5.95 (complex m, 1H), 4.30-4.25 (complex m, 2H), 3.93-3.89 (complex m, 1H), 3.71 (s, 3H), 1.57 (s, 3H), 1.30 (s, 3H), 1.22 (s, 3H);
^{13}C NMR (75 MHz, $CDCl_3$): δ 164.8 (C), 150.1 (CH), 138.1 (C), 136.2 (CH), 132.1 (CH), 113.2 (C), 82.9 (CH), 79.9 (CH), 51.7 (CH), 47.7 (C), 41.7 (CH_3), 25.8 (CH_3), 25.5 (CH_3), 19.0 (CH_3);
IR ν_{max} (KBr) 2977, 2949, 2934, 2905, 1718, 1456, 1437, 1380, 1371, 1263, 1242, 1211, 1162, 1058, 1037, 881, 755, 744, 717 cm^{-1};
MS (EI, 70 eV) *m/z*: 235 [(M-CH_3·)$^+$, 33%], 163 (90), 119 (75), 100 (96), 91 (64), 85 (100), 43 (85);
HREIMS Found: (M-CH_3·)$^+$, 235.0968. Calculated for $C_{14}H_{18}O_4$ (M-CH_3·)$^+$, 235.0970.
Optical rotation $[\alpha]_D^{19}$ +43.7 (*c* 1, $CHCl_3$).

Concentration of fraction B (R_f = 0.4 in 1:7:12 v/v/v MeOH/ethyl acetate/hexane) afforded β-hydroxyester **154b** (94 mg, 12% over two steps) as a white, crystalline solid that was identical, in all respects, with an authentic sample.

(3a*S*,4*S*,7*R*,7a*R*,8*R*,9*S*)-Methyl 8-hydroxy-3a,4,7,7a-tetrahydro-2,2,7-trimethyl-4,7-ethano-1,3-benzodioxol-9-carboxylate (154b).



154a **154b**

A solution of *β*-hydroxyester **154a** (59 mg, 220 μmol) in benzene (1.1 ml) containing DBU (58 μl, 220 μmol, 1 eq) was treated in exactly the same way as the mixture of **154a**, **155a** and **155b** described above. The resulting light-yellow solid (52 mg), which was comprised of a 1:3.4 mixture of *β*-hydroxyesters **154a** and **154b** (as determined by ^{1}H NMR analysis), was subjected to column chromatography (silica, 1:7:12 v/v/v MeOH/ethyl acetate/hexane) to afford two fractions, A and B.

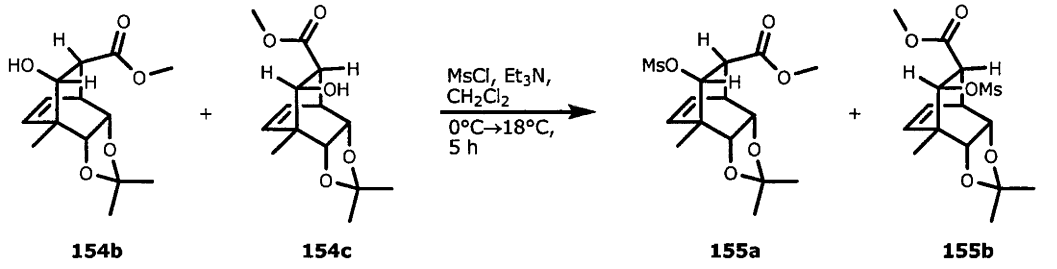
Concentration of fraction A (R_f = 0.4 in 1:7:12 v/v/v MeOH/ethyl acetate/hexane) yielded *β*-hydroxyester **154b** (29 mg, 49%) as a white, crystalline solid, m.p. 132.2-132.4°C.

^{1}H NMR (300 MHz, $CDCl_3$): *δ* 6.28 (ddd, *J* = 8.1, 6.7 and 0.8 Hz, 1H), 5.77 (dd, *J* = 8.1 and 1.2 Hz, 1H), 4.23 (ddd, *J* = 7.3, 3.4 and 1.2 Hz, 1H), 3.91 (dd, *J* = 3.3 and 1.2 Hz, 1H), 3.87 (dd, *J* = 7.3 and 1.2 Hz, 1H), 3.74 (s, 3H), 3.20-3.15 (complex m, 1H), 2.33 (t, *J* = 3.4 Hz, 1H), 1.59 (s, 1H), 1.37 (s, 3H), 1.31 (s, 3H), 1.25 (s, 3H);
^{13}C NMR (75 MHz, $CDCl_3$): *δ* 173.3 (C), 133.4 (CH), 131.2 (CH), 109.5 (C), 80.6 (CH), 75.7 (CH), 73.0 (CH), 52.4 (CH), 52.3 (CH_3), 44.9 (C), 36.4 (CH), 25.4 (CH_3), 24.9 (CH_3), 17.8 (CH_3);
IR ν_{max} (KBr) 3461, 2976, 2927, 2876, 1731, 1374, 1266, 1248, 1206, 1163, 1078, 1066, 1029, 882, 730 cm^{-1};
MS (EI, 70 eV) *m/z*: 268 ($M^{+\cdot}$, 8%), 253 [$(M-CH_3\cdot)^+$, 49], 133 (100), 109 (64), 108 (63), 105 (69), 100 (67), 43 (71);
HREIMS Found: $M^{+\cdot}$, 268.1312. Calculated for $C_{14}H_{20}O_5$ $M^{+\cdot}$, 268.1311.
Elemental analysis Found C, 62.69; H, 7.54; $C_{14}H_{20}O_5$ requires C, 62.67; H, 7.51%;
Optical rotation $[\alpha]_D^{19}$ +47.9 (*c* 1, $CHCl_3$).

A sample of this material was recrystallised and subjected to single-crystal X-ray analysis.

Concentration of fraction B (R_f = 0.4 in 1:7:12 v/v/v MeOH/ethyl acetate/hexane) afforded β-hydroxyester **154a** (16 mg, 27%) as a white, crystalline solid that was identical, in all respects, with an authentic sample.

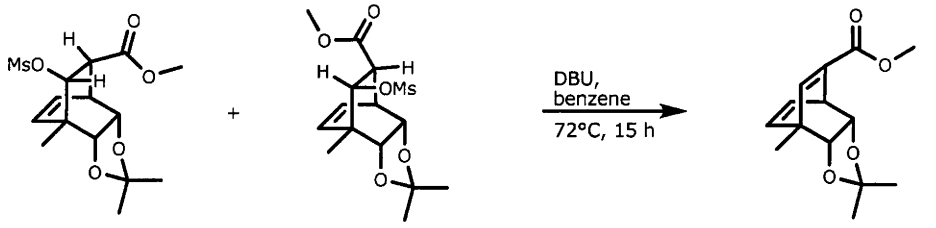
(3a*S*,4*S*,7*R*,7a*R*,8*R*,9*S*)-Methyl 8-methanesulfonyl-3a,4,7,7a-tetrahydro-2,2,7-trimethyl-4,7-ethano-1,3-benzodioxol-9-carboxylate (155a) and (3a*S*,4*S*,7*R*,7a*R*,8*S*,9*R*)-Methyl 8-methanesulfonyl-3a,4,7,7a-tetrahydro-2,2,7-trimethyl-4,7-ethano-1,3-benzodioxol-9-carboxylate (155b).



154b **154c** **155a** **155b**

Triethylamine (2.27 g, 22.44 mmol, 1.5 eq) was added to a solution of a *ca.* 4:1 mixture of alcohols **154b** and **154c** (4.01 g, 14.96 mmol) in dichloromethane (75 ml) and the resulting mixture was cooled to 0°C then treated, dropwise, with mesyl chloride (1.89 g, 16.46 mmol, 1.1 eq). The ensuing mixture was stirred at 0°C for 1 h then at 18°C for 4 h after which it was diluted with dichloromethane (25 ml). The resulting solution was then washed with ice-cold water (1 x 100 ml), hydrochloric acid (1 x 100 ml of a 2 M aq. solution), sodium hydrogen carbonate (1 x 100 ml of a saturated aq. solution) and brine (1 x 100 ml), before being dried (magnesium sulfate), filtered and concentrated under reduced pressure to give an off-white solid (4.89 g). This material, which was comprised of a *ca.* 4:1 mixture of mesylates **155a** and **155b** as determined by ^{1}H NMR analysis, was used directly in the next step of the reaction sequence.

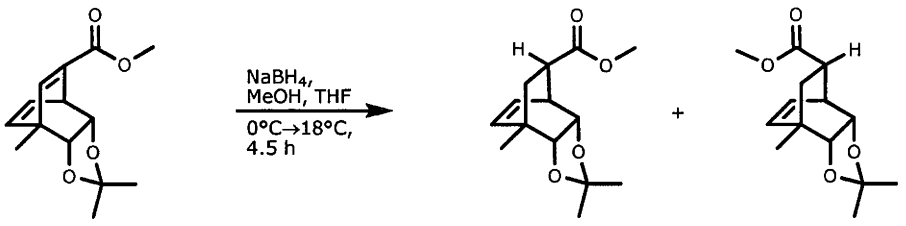
(3a*S*,4*S*,7*R*,7a*R*)-Methyl 3a,4,7,7a-tetrahydro-2,2,7-trimethyl-4,7-etheno-1,3-benzodioxol-9-carboxylate (156).



155a **155b** **156**

DBU (2.40 ml, 16.07 mmol, 2.6 eq) was added to a solution of a *ca.* 4:1 mixture of **155a** and **155b** (2.14 g, 6.18 mmol) in benzene (30 ml) and the resulting mixture heated to 72°C for 15 h then cooled to 18°C and diluted with dichloromethane (20 ml). The resulting solution was washed with hydrochloric acid (1 x 50 ml of a 2 M aq. solution), sodium hydrogen carbonate (1 x 50 ml of a saturated aq. solution) and brine (1 x 50 ml) then dried (magnesium sulfate), filtered and concentrated under reduced pressure. The yellow oil (1.62 g) thus obtained was subjected to column chromatography (silica, 1:7:12 v/v/v MeOH/ethyl acetate/hexane) and concentration of the appropriate fractions then gave olefin **156** (1.42 g, 92%) as a light-yellow oil that was identical, in all respects, with an authentic sample.

(3a*S*,4*S*,7*S*,7a*R*,9*R*)-Methyl 3a,4,7,7a-tetrahydro-2,2,7-trimethyl-4,7-ethano-1,3-benzodioxol-9-carboxylate (157a) and (3a*S*,4*S*,7*S*,7a*R*,9*S*)-Methyl 3a,4,7,7a-tetrahydro-2,2,7-trimethyl-4,7-ethano-1,3-benzodioxol-9-carboxylate (157b).



156 **157a** **157b**

A solution of α,β-unsaturated ester **156** (897 mg, 3.59 mmol) in THF/MeOH (124 ml of a 7:1 v/v mixture) was cooled to 0°C and sodium borohydride (489 mg, 12.93 mmol, 3.6 eq) was then added in one portion. The ensuing mixture was stirred at 0°C→18°C for 4.5 h then re-cooled to 0°C and quenched with ammonium chloride (100 ml of a saturated aq. solution). The resulting mixture was extracted with dichloromethane (3 x 50 ml), and the combined organic extracts were washed with brine (1 x 100 ml) before being dried (magnesium sulfate), filtered and concentrated under reduced pressure. The ensuing light-yellow oil was subjected to column chromatography (silica, 1:7:12 v/v/v MeOH/ethyl acetate/hexane) to afford two fractions, A and B.

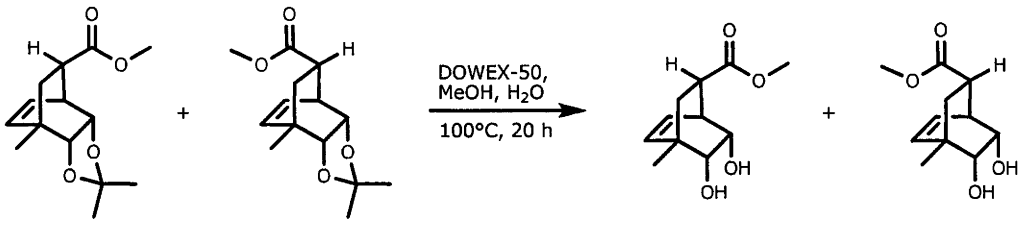
Concentration of fraction A (R_f = 0.8 in 1:7:12 v/v/v MeOH/ethyl acetate/hexane) gave compound **157a** (333 mg, 37%) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.11 (ddd, J = 8.1, 6.3 and 0.9 Hz, 1H), 5.83 (dd, J = 8.1 and 0.9 Hz, 1H), 4.22 (ddd, J = 7.2, 3.3 and 0.9 Hz, 1H), 3.88 (dd, J = 7.2 and 1.2 Hz, 1H), 3.69 (s, 3H), 3.16-3.10 (complex m, 1H), 2.47 (ddd, J = 11.4, 5.4 and 3.0 Hz, 1H), 1.65 (dd, J = 13.5 and 5.4 Hz, 1H), 1.31 (dd, J = 13.5 and 11.4 Hz, 1H), 1.29 (s, 3H), 1.25 (s, 3H), 1.23 (s, 3H);
^{13}C NMR (75 MHz, $CDCl_3$): δ 174.8 (C), 136.7 (CH), 130.0 (CH), 107.9 (C), 82.6 (CH), 76.1 (CH), 52.0 (CH_3), 40.8 (CH), 38.5 (C), 37.3 (CH), 31.4 (CH_2), 25.4 (CH_3), 24.9 (CH_3), 21.5 (CH_3);
IR ν_{max} (KBr) 2976, 2955, 2936, 2900, 2873, 1733, 1458, 1435, 1374, 1343, 1297, 1265, 1239, 1205, 1165, 1070, 1055, 1021, 997, 885, 724 cm^{-1};
MS (EI, 70 eV) *m/z*: 252 ($M^{+\cdot}$, 13%), 237 [$(M\text{-}CH_3\cdot)^+$, 44], 221 [$(M\text{-}CH_3O\cdot)^+$, 16], 194 (66), 135 (100), 134 (60), 117 (55), 105 (55), 91 (64);
HREIMS Found: $M^{+\cdot}$, 252.1357. Calculated for $C_{14}H_{20}O_4$ $M^{+\cdot}$, 252.1362.
Optical rotation $[\alpha]_D^{18}$ -1.6 (*c* 1, $CHCl_3$).

Concentration of fraction B (R_f = 0.8 in 1:7:12 v/v/v MeOH/ethyl acetate/hexane) yielded compound **157b** (398 mg, 44%) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.96 (dd, J = 8.1 and 6.3 Hz, 1H), 5.88 (dd, J = 8.1 and 0.6 Hz, 1H), 4.24 (ddd, J = 7.2, 3.3 and 0.9 Hz, 1H), 3.84 (dd, J = 7.2 and 1.2 Hz, 1H), 3.65 (s, 3H), 3.23-3.18 (complex m, 1H), 2.50 (ddd, J = 10.2, 5.1 and 2.4 Hz, 1H), 1.59 (dd, J = 13.5 and 5.1 Hz, 1H), 1.39 (dd, J = 13.5 and 10.2 Hz, 1H), 1.30 (s, 3H), 1.26 (s, 3H), 1.26 (s, 3H);
^{13}C NMR (75 MHz, $CDCl_3$): δ 174.6 (C), 136.9 (CH), 127.8 (CH), 108.6 (C), 82.7 (CH), 78.8 (CH), 52.0 (CH_3), 39.6 (CH), 38.1 (C), 37.5 (CH), 32.3 (CH_2), 25.5 (CH_3), 25.0 (CH_3), 21.5 (CH_3);
IR ν_{max} (KBr) 2971, 2956, 2931, 2873, 1738, 1373, 1285, 1254, 1203, 1167, 1063, 885, 714 cm^{-1};
MS (EI, 70 eV) *m/z*: 252 ($M^{+\bullet}$, 7%), 237 [$(M-CH_3\bullet)^+$, 61], 221 [$(M-CH_3O\bullet)^+$, 27], 194 (84), 162 (84), 135 (100), 134 (83), 117 (70), 105 (70), 100 (81), 93 (70);
HREIMS Found: $M^{+\bullet}$, 252.1363. Calculated for $C_{14}H_{20}O_4$ $M^{+\bullet}$, 252.1362.
Optical rotation $[\alpha]_D^{19}$ -26.2 (*c* 1, $CHCl_3$).

(1*S*,2*R*,4*S*,5*R*,6*S*)-Methyl 5,6-dihydroxy-4-methylbicyclo[2.2.2]oct-7-ene-2-carboxylate (158a) and (1*S*,2*S*,4*S*,5*R*,6*S*)-Methyl 5,6-dihydroxy-4-methylbicyclo[2.2.2]oct-7-ene-2-carboxylate (158b).



157a **157b** **158a** **158b**

DOWEX-50 was activated by successive washing with sodium hydrogen carbonate (saturated aq. solution), water, hydrochloric acid (1 M aq. solution) and water. The activated resin (890 mg) was then added to a solution of a 1:1.2 mixture of acetonides **157a** and **157b** (887 mg, 3.52 mmol) in MeOH/water (18 ml of a 5:1 v/v mixture) and the resulting suspension was heated to 100°C for 20 h then cooled to room temperature, the resin DOWEX filtered off and washed with methanol (3 x 15 ml). The combined filtrates were concentrated to *ca.* 1/3 of the original volume and sodium chloride (30 ml of a 1.5 M aq. solution) added. The resulting aqueous solution was extracted with dichloromethane (5 x 30 ml) then the combined organic phases were washed with brine (1 x 30 ml) before being dried (magnesium sulfate), filtered and concentrated under reduced pressure. The yellow oil (653 mg) thus obtained was subjected to column chromatography (silica, 1:1 v/v ethyl acetate/hexane) to afford three fractions, A, B and C.

Concentration of fraction A (R_f = 0.8 in 1:1 v/v ethyl acetate/hexane) gave a 1:1.1 mixture of starting materials **157a** and **157b** (87 mg, 10% recovery) as a clear, colourless oil. This material was identical, in all respects, with an authentic sample.

Concentration of fraction B (R_f = 0.3 in 1:1 v/v ethyl acetate/hexane) afforded diol **158a** (250 mg, 34%) as a clear, colourless oil.

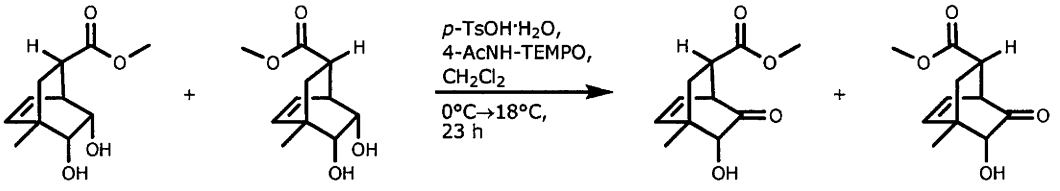
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.29 (ddd, J = 8.2, 6.9 and 0.7 Hz, 1H), 5.97 (dd, J = 8.2 and 0.7 Hz, 1H), 3.99 (dd, J = 7.5 and 2.2 Hz, 1H), 3.70 (s, 3H), 3.58 (d, J = 7.5 Hz, 1H), 3.08-3.03 (complex m, 1H), 2.40-2.80 (broad s, 2H), 2.42 (ddd, J = 11.6, 5.9 and 2.9 Hz, 1H), 1.71 (dd, J = 13.6 and 5.9 Hz, 1H), 1.35 (dd, J = 13.6 and 11.6 Hz, 1H), 1.27 (s, 3H);
^{13}C NMR (75 MHz, $CDCl_3$): δ 174.8 (C), 137.6 (CH), 131.5 (CH), 74.7 (CH), 68.2 (CH), 52.1 (CH_3), 41.5 (CH), 40.1 (CH), 39.9 (C), 32.3 (CH_2), 21.3 (CH_3);

IR ν_{max} (KBr) 3395, 2954, 2872, 1731, 1458, 1435, 1373, 1303, 1204, 1174, 1069, 1032, 980, 724 cm^{-1};
MS (ESI, +ve ion mode) *m/z*: 235 [$(M+Na)^+$, 100%], 195 (19), 163 (42), 135 (31);
HRESMS Found: $(M+Na)^+$, 235.0942. Calculated for $C_{11}H_{16}O_4$ $(M+Na)^+$, 235.0946.
Optical rotation $[\alpha]_D^{17}$ -15.4 (*c* 1, $CHCl_3$).

Concentration of fraction C (R_f = 0.2 in 1:1 v/v ethyl acetate/hexane) gave diol **158b** (261 mg, 35%) as a white, crystalline solid, m.p. 80-82°C (recrystallised from benzene).

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.14 (dd, *J* = 8.2 and 6.6 Hz, 1H), 6.00 (d, *J* = 8.2 Hz, 1H), 3.98-3.91 (complex m, 1H), 3.65 (s, 3H), 3.51 (t, *J* = 7.0 Hz, 1H), 3.20-3.14 (complex m, 1H), 2.67 (d, *J* = 6.0 Hz, 1H), 2.60 (ddd, *J* = 9.9, 5.1 and 2.4 Hz, 1H), 2.40 (d, *J* = 7.0 Hz, 1H), 1.61 (dd, *J* = 13.5 and 5.1 Hz, 1H), 1.49 (dd, *J* = 13.5 and 9.9 Hz, 1H), 1.28 (s, 3H);
^{13}C NMR (75 MHz, $CDCl_3$): δ 174.5 (C) 137.7 (CH), 129.3 (CH), 74.4 (CH), 70.8 (CH), 52.0 (CH_3), 40.3 (CH), 40.2 (CH), 39.5 (C), 33.4 (CH_2), 21.2 (CH_3);
IR ν_{max} (KBr) 3426, 2954, 2928, 2898, 2869, 1732, 1454, 1435, 1400, 1373, 1292, 1201, 1176, 1143, 1114, 1093, 1060, 1032, 1017, 995, 963, 905, 883, 836, 729, 710 cm^{-1};
MS (EI, 70 eV) *m/z*: 212 ($M^{+\bullet}$, 2%), 181 [$(M-CH_3O\bullet)^+$, 23], 153 (66), 152 (93), 94 (47), 93 (100), 92 (79), 91 (67), 77 (62);
HREIMS Found: $M^{+\bullet}$, 212.1039. Calculated for $C_{11}H_{16}O_4$ $M^{+\bullet}$, 212.1049.
Elemental analysis Found C, 62.30; H, 7.61; $C_{11}H_{16}O_4$ requires C, 62.25; H, 7.60%;
Optical rotation $[\alpha]_D^{19}$ -36.0 (*c* 0.5, $CHCl_3$).

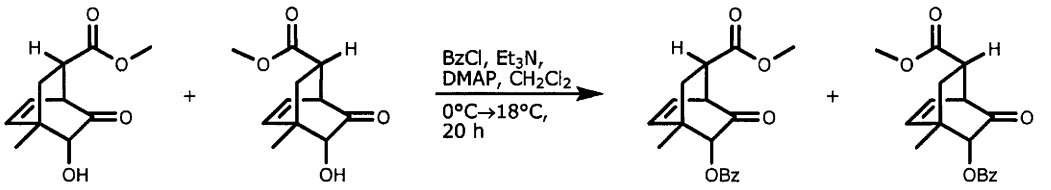
(1*S*,2*R*,4*S*,5*R*)-Methyl 5-hydroxy-4-methyl-6-oxobicyclo[2.2.2]oct-7-ene-2-carboxylate (159a) and (1*S*,2*S*,4*S*,5*R*)-Methyl 5-hydroxy-4-methyl-6-oxobicyclo[2.2.2]oct-7-ene-2-carboxylate (159b).



158a **158b** **159a** **159b**

A magnetically stirred solution of a *ca.* 1:1 mixture of diols **158a** and **158b** (2.34 g, 11.03 mmol) in dichloromethane (260 ml) was cooled to 0°C then treated, in one portion, with *p*-TsOH·H_2O (4.62 g, 24.27 mmol, 2.2 eq) and then, in six equal portions over 2.5 h, with 4-AcNH-TEMPO (5.18 g, 24.27 mmol, 2.2 eq). The resulting mixture was allowed to slowly warm to 18°C and after 20.5 h it was quenched with sodium hydrogen carbonate (130 ml of a saturated aq. solution). The separated aqueous phase was extracted with dichloromethane (3 x 130 ml) then the combined organic phases were washed with brine (1 x 130 ml) before being dried (magnesium sulfate), filtered and concentrated under reduced pressure. The resulting orange-red semi-solid was subjected to column chromatography (silica, 1:2 v/v ethyl acetate/hexane) and concentration of the appropriate fractions (R_f = 0.5 in 1:1 v/v ethyl acetate/hexane) gave a chromatographically inseparable and 1:1.3 mixture of acyloins **159a** and **159b** (2.02 g) as a clear, colourless oil that was used directly in the next step of the reaction sequence.

(1*S*,2*R*,4*S*,5*R*)-Methyl 5-(benzoyloxy)-4-methyl-6-oxobicyclo[2.2.2]oct-7-ene-2-carboxylate (160a) and (1*S*,2*S*,4*S*,5*R*)-Methyl 5-(benzoyloxy)-4-methyl-6-oxobicyclo[2.2.2]oct-7-ene-2-carboxylate (160b).



159a **159b** **160a** **160b**

A magnetically stirred solution of a 1:1.3 mixture of acyloins **159a** and **159b** (2.00 g, 9.52 mmol) in dichloromethane (300 ml) was cooled to 0°C then triethylamine (6.64 ml, 47.60 mmol, 5 eq) and DMAP (120 mg, 0.95 mmol, 0.1 eq) were added, followed by benzoyl chloride (2.21 ml, 19.04 mmol, 2 eq). The resulting mixture was allowed to slowly warm to 18°C. After 20 h the reaction mixture was quenched with sodium hydrogen carbonate (150 ml of a saturated aq. solution) and the separated aqueous phase was extracted with dichloromethane (3 x 150 ml). The combined organic phases were then washed with brine (1 x 150 ml) before being dried (magnesium sulfate), filtered and concentrated under reduced pressure to provide a yellow/red oil comprised, as determined by ^{1}H NMR analysis, of a 1:1.2 mixture of esters **160a** and **160b**. This material was subjected to column chromatography (silica, 1:2 v/v ethyl acetate/hexane) to afford two fractions, A and B.

Concentration of fraction A (R_f = 0.6 in 1:2 v/v ethyl acetate/hexane) afforded a solid (1.49 g) that was recrystallised (benzene/hexane) to yield compound **160b** (1.26 g, 42%) as a white, crystalline solid, m.p. 118°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.02-7.98 (complex m, 2H), 7.60-7.53 (complex m, 1H), 7.46-7.40 (complex m, 2H), 6.27 (dd, J = 8.0 and 1.5 Hz, 1H), 6.22 (dd, J = 8.0 and 6.2 Hz, 1H), 5.17 (s, 1H), 3.71 (s, 3H), 3.67 (ddd, J = 6.2, 2.0 and 1.5 Hz, 1H), 3.12 (ddd, J = 9.9, 6.0 and 2.0 Hz, 1H), 2.08 (dd, J = 13.7 and 9.9 Hz, 1H), 1.99 (dd, J = 13.7 and 6.0 Hz, 1H), 1.27 (s, 3H);
^{13}C NMR (75 MHz, $CDCl_3$): δ 203.5 (C), 173.0 (C), 166.1 (C), 140.4 (CH), 133.4 (CH), 129.9 (CH), 129.1 (C), 128.4 (CH), 125.0 (CH), 73.5 (CH), 52.5 (CH_3), 49.7 (CH), 40.9 (C), 38.2 (CH), 34.8 (CH_2), 20.0 (CH_3);
IR ν_{max} (KBr) 2954, 2934, 1743, 1726, 1452, 1328, 1317, 1269, 1194, 1178, 1110, 1070, 1032, 710 cm^{-1};
MS (EI, 70 eV) *m/z*: 314 ($M^{+\cdot}$, 38%), 283 [$(M-CH_3O\cdot)^+$, 13], 164 (63), 152 (43), 106 (67), 105 (100), 93 (70), 77 (87);

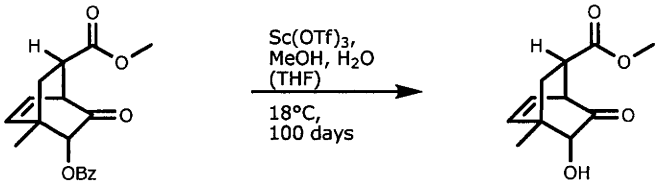
HREIMS Found: $M^{+\bullet}$, 314.1154. Calculated for $C_{18}H_{18}O_5$ $M^{+\bullet}$, 314.1154.
Elemental analysis Found C, 69.00; H, 5.84; $C_{18}H_{18}O_5$ requires C, 68.78; H, 5.77%;
Optical rotation $[\alpha]_D^{19}$ +267.8 (*c* 1, $CHCl_3$).

Concentration of fraction B (R_f = 0.5 in 1:2 v/v ethyl acetate/hexane) afforded a white solid (1.31 g) that was recrystallised (benzene/hexane) to give compound **160a** (795 mg, 27%) as a white, crystalline solid, m.p. 106°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.04-7.99 (complex m, 2H), 7.60-7.53 (complex m, 1H), 7.46-7.39 (complex m, 2H), 6.33-6.24 (complex m, 2H), 5.34 (s, 1H), 3.73 (s, 3H), 3.49 (ddd, *J* = 6.2, 2.9 and 1.8 Hz, 1H), 2.82 (ddd, *J* = 12.0, 4.8 and 2.9 Hz, 1H), 2.07 (dd, *J* = 13.6 and 4.8 Hz, 1H), 1.87 (dd, *J* = 13.6 and 12.0 Hz, 1H), 1.27 (s, 3H);
^{13}C NMR (125 MHz, $CDCl_3$): δ 203.2 (C), 174.4 (C), 165.9 (C), 140.9 (CH), 133.2 (CH), 129.9 (CH), 129.4 (C), 128.4 (CH), 126.6 (CH), 74.0 (CH), 52.6 (CH_3), 50.2 (CH), 41.2 (CH), 41.0 (C), 35.2 (CH_2), 20.0 (CH_3);
IR ν_{max} (KBr) 2961, 2935, 1746, 1724, 1451, 1435, 1355, 1324, 1267, 1254, 1204, 1177, 1161, 1110, 1097, 1070, 1030, 710 cm^{-1};
MS (EI, 70 eV) *m/z*: 314 ($M^{+\bullet}$, 2%), 164 (7), 105 (100), 93 (9), 77 (20);
HREIMS Found: $M^{+\bullet}$, 314.1159. Calculated for $C_{18}H_{18}O_5$ $M^{+\bullet}$, 314.1154.
Elemental analysis Found C, 68.58; H, 5.72; $C_{18}H_{18}O_5$ requires C, 68.78; H, 5.77%;
Optical rotation $[\alpha]_D^{19}$ +321.7 (*c* 0.7, $CHCl_3$).

A sample of the recrystallised material was subjected to single-crystal X-ray analysis.

(1*S*,2*R*,4*S*,5*R*)-Methyl 5-hydroxy-4-methyl-6-oxobicyclo[2.2.2]oct-7-ene-2-carboxylate (159a).



160a **159a**

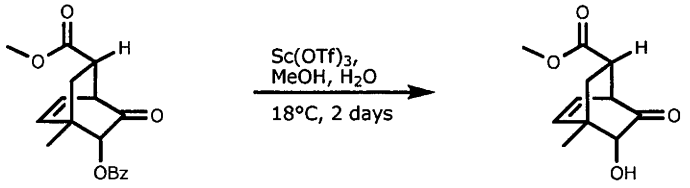
Distilled water (0.5 ml) then scandium(III) triflate (20 mg, 41 μmol, 0.21 eq) were added to a magnetically stirred solution of ester **160a** (60 mg, 191 μmol) in MeOH/THF (3 ml of a 2:1 v/v mixture). The reaction was stored at 18°C for ≥100 days after which it was quenched with distilled water (1 ml) then diluted with dichloromethane (3 ml). The separated aqueous phase was extracted with dichloromethane (2 x 3 ml) then the combined organic phases were dried (magnesium sulfate), filtered and concentrated under reduced pressure. The white semi-solid (53 mg) thus obtained was subjected to column chromatography (silica, 1:1 v/v ethyl acetate/hexane) to afford two fractions, A and B.

Concentration of fraction A (R_f = 0.6 in 1:1 v/v ethyl acetate/hexane) yielded starting material **160a** (10 mg, 17% recovery) as a white, crystalline solid that was identical, in all respects, with an authentic sample.

Concentration of fraction B (R_f = 0.5 in 1:1 v/v ethyl acetate/hexane) afforded acyloin **159a** (16 mg, 40%) as a clear, colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.19-6.13 (complex m, 2H), 3.69 (s, 3H), 3.63 (s, 1H), 3.41-3.38 (complex m, 1H), 2.84-2.74 (broad s, 1H, partly obscured), 2.76 (ddd, J = 11.5, 5.1 and 2.9 Hz, 1H), 1.86-1.76 (complex m, 2H), 1.35 (s, 3H);
^{13}C NMR (125 MHz, $CDCl_3$): δ 209.6 (C), 175.2 (C), 141.7 (CH), 125.7 (CH), 74.3 (CH), 52.5 (CH_3), 49.2 (CH), 41.7 (C), 40.7 (CH), 35.7 (CH_2), 19.8 (CH_3);
IR ν_{max} (KBr) 3473, 2957, 2933, 2872, 1737, 1734, 1456, 1436, 1354, 1309, 1277, 1244, 1206, 1177, 1168, 1144, 1120, 1074, 1022, 983, 975, 897, 886, 862, 839, 782, 726, 703 cm^{-1};
MS (EI, 70 eV) *m/z*: 210 ($M^{+\bullet}$, 4%), 182 (34), 150 (29), 122 (37), 105 (35), 93 (100), 79 (36), 77 (37);
HREIMS Found: $M^{+\bullet}$, 210.0896. Calculated for $C_{11}H_{14}O_4$ $M^{+\bullet}$, 210.0892.
Optical rotation $[\alpha]_D^{20}$ +298.8 (*c* 0.75, $CHCl_3$).

(1*S*,2*S*,4*S*,5*R*)-Methyl 5-hydroxy-4-methyl-6-oxobicyclo[2.2.2]oct-7-ene-2-carboxylate (159b).



160b **159b**

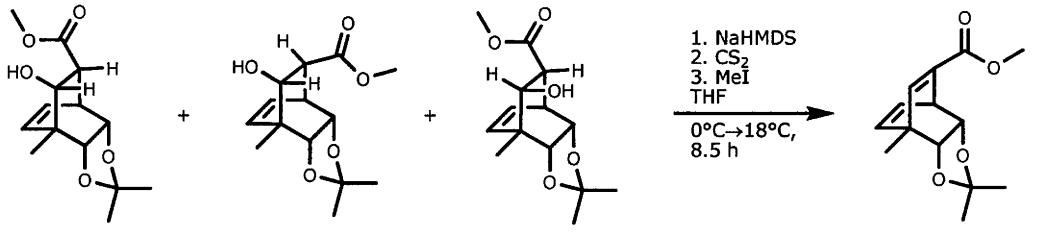
Distilled water (0.5 ml) then scandium(III) triflate (20 mg, 41 μmol, 0.21 eq) were added to a solution of ester **160b** (60 mg, 191 μmol) in methanol (2 ml). The reaction was stirred at 18°C for 2 days then quenched with distilled water (2 ml) and diluted with dichloromethane (5 ml). The separated aqueous phase was extracted with dichloromethane (2 x 5 ml) then the combined organic phases were dried (magnesium sulfate), filtered and concentrated under reduced pressure. The clear, colourless oil (73 mg) thus obtained was subjected to column chromatography (silica, 1:1 v/v ethyl acetate/hexane) to afford two fractions, A and B.

Concentration of fraction A (R_f = 0.7 in 1:1 v/v ethyl acetate/hexane) yielded starting material **160b** (37 mg, 62% recovery) as a white, crystalline solid that was identical, in all respects, with an authentic sample.

Concentration of fraction B (R_f = 0.5 in 1:1 v/v ethyl acetate/hexane) afforded acyloin **159b** (11 mg, 27%) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.16 (d, J = 7.8 Hz, 1H), 6.10 (dd, J = 7.8 and 6.4 Hz, 1H), 3.70 (s, 3H), 3.59 (ddd, J = 6.4, 2.1 and 1.4 Hz, 1H), 3.45 (s, 1H), 3.01 (ddd, J = 9.1, 7.3 and 2.1 Hz, 1H), 1.97-1.82 (complex m, 2H), 1.36 (s, 3H) , signal due to hydroxyl proton not observed;
^{13}C NMR (75 MHz, $CDCl_3$): δ 209.4 (C), 173.2 (C), 141.2 (CH), 124.4 (CH), 74.2 (CH), 52.4 (CH_3), 48.9 (CH), 41.8 (C), 37.9 (CH), 35.2 (CH_2), 19.9 (CH_3);
IR ν_{max} (KBr) 3474, 2957, 2933, 1732, 1459, 1437, 1360, 1287, 1230, 1198, 1181, 1138, 1100, 1076, 1018, 967, 902, 886, 835, 770, 715, 667, 628 cm^{-1};
MS (EI, 70 eV) *m/z*: 210 ($M^{+\cdot}$, 32%), 179 [$(M-CH_3O\cdot)^+$, 14], 151 (38), 150 (47), 105 (65), 93 (100), 79 (48), 77 (37), 45 (50);
HREIMS Found: $M^{+\cdot}$, 210.0889. Calculated for $C_{11}H_{14}O_4$ $M^{+\cdot}$, 210.0892.

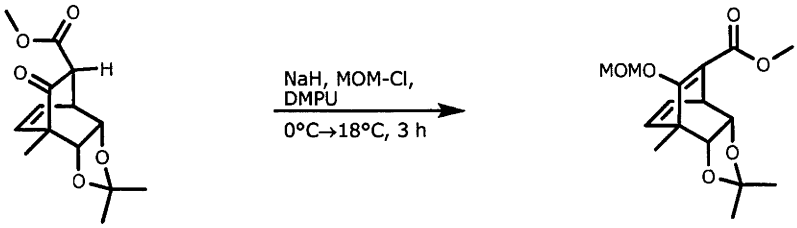
(3a*S*,4*S*,7*R*,7a*R*)-Methyl 3a,4,7,7a-tetrahydro-2,2,7-trimethyl-4,7-etheno-1,3-benzodioxol-9-carboxylate (156).



154a **154b** **154c** **156**

A solution of a mixture of β-hydroxyesters **154a-c** (77 mg, 290 μmol) in THF (2.90 ml) was cooled to 0°C then NaHMDS (580 μl of a 1 M solution in THF, 580 μmmol, 2 eq) was added dropwise. The ensuing mixture was stirred at 0°C for 1.5 h and then at 18°C for 0.5 h, before being recooled to 0°C. Carbon disulfide (30 μl, 580 μmol, 2 eq) was added dropwise then the reaction was stirred at 0°C for 1.5 h and at 18°C for 0.5 h, after which it was again recooled to 0°C. Iodomethane (40 μl, 610 μmol, 2.1 eq) was added dropwise and the mixture was stirred at 0°C for 1.5 h then at 18°C for 3 h before it was diluted with diethyl ether (5 ml) then washed with distilled water (1 x 5 ml), hydrochloric acid (1 x 5 ml of a 1 M aq. solution) and brine (1 x 5 ml). The organic layer was dried (magnesium sulfate), filtered and concentrated under reduced pressure to reveal a yellow-orange oil (39 mg) that was subjected to column chromatography (silica, 1:4 v/v ethyl acetate/hexane). Concentration of the appropriate fractions (R_f = 0.6 in 1:4 v/v ethyl acetate/hexane) then gave α,β-unsaturated ester **156** (14 mg, 19%) as a light-yellow oil and instead of the expected deoxygenation products. The oil containing ester **156** was identical, in all respects, with an authentic sample.

Methyl (3a*S*,4*S*,7*S*,7a*R*)-8-(methoxymethoxy)-3a,4,7,7a-tetrahydro-2,2,7-trimethyl-4,7-etheno-1,3-benzodioxol-9-carboxylate (167)



151 **167**

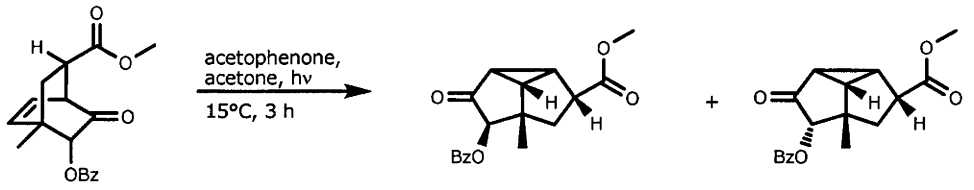
A sample of DMPU (3.75 ml) was cooled to 0°C and sodium hydride (165 mg of a 60% w/w dispersion in paraffin oil, 4.13 mmol, 1.1 eq) was added. After gas evolution had subsided, a solution of *β*-ketoester **151** (998 mg, 3.75 mmol) in DMPU (15 ml)* was added and the resulting reaction mixture was warmed to 18°C and stirred at this temperature for 1 h. The ensuing red-coloured mixture was cooled back to 0°C and MOM-Cl (0.34 ml 4.50 mmol, 1.2 eq) was added dropwise. The cooling bath was then removed and the reaction mixture stirred at 18°C whereby the colour of the reaction gradually changed to a light-yellow tone. After 1.5 h the reaction mixture was cooled to 0°C and poured into sodium hydrogen carbonate (10 ml of a saturated aq. solution) maintained at 0°C. The yellowish suspension was extracted with hexane (3 x 20 ml) and the combined organic layers were washed with distilled water (4 x 10 ml) then dried (magnesium sulfate), filtered and concentrated under reduced pressure to give enol ether **167** (747 mg, 64%) as a clear, colourless oil.

R_f = 0.4 in 1:4 v/v ethyl acetate/hexane;
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.35 (ddd, J = 7.0, 6.3 and 0.6 Hz, 1H), 5.94 (ddd, J = 7.0, 1.8 and 1.1 Hz, 1H), 5.12 (d, J = 6.1 Hz, 1H), 5.04 (d, J = 6.1 Hz, 1H), 4.45 (ddd, J = 7.0, 3.7 and 0.6 Hz, 1H), 4.22-4.17 (complex m, 1H), 4.09 (dd, J = 7.0 and 1.1 Hz, 1H), 3.70 (s, 3H), 3.48 (s, 3H), 1.51 (s, 3H), 1.32 (s, 3H), 1.27 (s, 3H);
^{13}C NMR (75 MHz, $CDCl_3$): δ 173.2 (C), 164.6 (C), 135.7 (CH), 133.1 (CH), 113.4 (C), 109.8 (C), 101.9 (CH_2), 82.9 (CH), 80.2 (CH), 57.4 (CH_3), 51.5 (CH_3), 51.3 (C), 41.6 (CH), 25.9 (CH_3), 25.6 (CH_3), 15.4 (CH_3);
MS (EI, 70 eV) *m/z*: 310 ($M^{+\cdot}$, 3%), 295 [$(M-CH_3\cdot)^+$, 10], 279 [$(M-CH_3O\cdot)^+$, 11], 266 (8), 252 (12), 179 (54), 100 (95), 91 (57), 85 (99), 45 (100), 43 (53);
HREIMS Found: $M^{+\cdot}$, 310.1413. Calculated for $C_{16}H_{22}O_6$ $M^{+\cdot}$, 310.1416.

This material was used directly in the next step of the reaction sequence.

* Sonification was necessary to dissolve the solid.

Methyl (1*S*,2*R*,3*R*,5*S*,6*R*,8*R*)-6-(benzoyloxy)-7-oxo-5-methyltricyclo [3.3.0.0^{2,8}]octan-3-carboxylate (169a) and Methyl (1*S*,2*R*,3*R*,5*S*,6*S*,8*R*)-6-(benzoyloxy)-7-oxo-5-methyltricyclo[3.3.0.0^{2,8}]octan-3-carboxylate (169b).



160a **169a** **169b**

A deoxygenated solution of ester **160a** (200 mg, 0.64 mmol) and acetophenone (0.22 ml, 1.92 mmol, 3 eq) in acetone (250 ml) was placed in a quartex immersion well photoreactor (Ace Glass Inc., 500 ml) equipped with a Pyrex filter. The mixture was subjected to irradiation with a Hanovia 450W medium pressure quartz mercury-vapour lamp. After 3 h the reaction mixture was removed from the reactor and the solvent was evaporated under reduced pressure to give a yellowish oil (459 mg). This was subjected to column chromatography (silica, 1:2 v/v ethyl acetate/hexane) thus affording two fractions, A and B.

Concentration of fraction A (R_f = 0.3 in 1:2 v/v ethyl acetate/hexane) gave diquinane **169a** (12 mg, 6%) as a white, crystalline solid, m.p. 143-146°C.

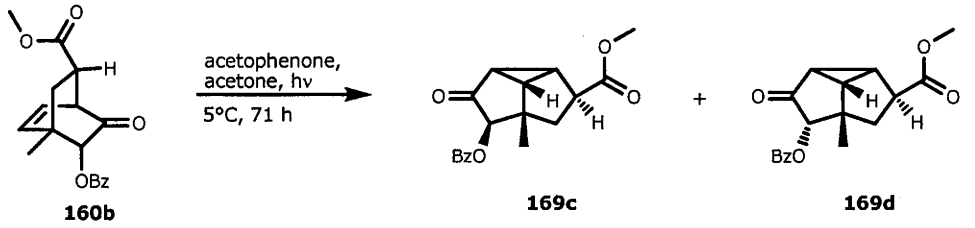
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06-8.02 (complex m, 2H), 7.60-7.53 (complex m, 1H), 7.47-7.40 (complex m, 2H), 5.26 (s, 1H), 3.67 (s, 3H), 3.52 (ddd, J = 8.5, 6.7 and 3.7 Hz, 1H), 2.66-2.61 (complex m, 1H), 2.46-2.37 (complex m, 1H), 2.36-2.31 (complex m, 2H), 2.23 (dd, J = 9.8 and 5.1 Hz, 1H), 1.30 (s, 3H);
^{13}C NMR (75 MHz, $CDCl_3$): δ 208.7 (C), 173.7 (C), 165.5 (C), 133.2 (CH), 129.8 (CH), 129.4 (C), 128.4 (CH), 83.3 (CH), 52.0 (CH_3), 50.2 (C), 46.5 (CH_2), 44.3 (CH), 41.9 (CH), 38.3 (CH), 36.9 (CH), 19.4 (CH_3);
IR ν_{max} (KBr) 2952, 1738, 1732, 1725, 1451, 1328, 1267, 1205, 1176, 1106, 1096, 1070, 1026, 965, 711 cm^{-1};
MS (EI, 70 eV) *m/z*: 314 ($M^{+\cdot}$, 3%), 283 [$(M-CH_3O\cdot)^+$, 6], 209 (19), 164 (24), 149 (18), 106 (33), 105 (100), 93 (47), 77 (76);
HREIMS Found: $M^{+\cdot}$, 314.1155. Calculated for $C_{18}H_{18}O_5$ $M^{+\cdot}$, 314.1154.
Elemental analysis Found C, 68.89; H, 5.90; $C_{18}H_{18}O_5$ requires C, 68.78; H, 5.77%;
Optical rotation $[\alpha]_D^{19}$ +143.5 (*c* 1, $CHCl_3$).

A sample of this material was recrystallised (hexane/benzene) to give crystals suitable for single-crystal X-ray analysis.

Concentration of fraction B (R_f = 0.3 in 1:2 v/v ethyl acetate/hexane) gave diquinane **169b** (127 mg, 63%) as a white oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.20-8.13 (complex m, 2H), 7.62-7.54 (complex m, 1H), 7.50-7.43 (complex m, 2H), 5.42 (s, 1H), 3.67 (s, 3H), 3.56-3.48 (complex m, 1H), 2.69 (d, J = 14.0 Hz, 1H), 2.46-2.36 (complex m, 2H), 2.11-1.98 (complex m, 2H), 1.45 (s, 3H);
^{13}C NMR (75 MHz, $CDCl_3$): δ 204.7 (C), 172.8 (C), 165.5 (C), 133.3 (CH), 130.1 (CH), 129.3 (C), 128.4 (CH), 81.4 (CH), 52.0 (CH_3), 48.9 (C), 44.9 (CH), 40.4 (CH_2), 35.5 (CH), 32.5 (CH), 31.9 (CH), 24.0 (CH_3);
IR ν_{max} (KBr) 2949, 2928, 1736, 1731, 1726, 1452, 1331, 1271, 1210, 1179, 1117, 1096, 1072, 712 cm^{-1};
MS (EI, 70 eV) *m/z*: 314 ($M^{+\bullet}$, 1%), 209 (6), 164 (7), 149 (6), 105 (100), 93 (23), 77 (37);
HREIMS Found: $M^{+\bullet}$, 314.1154. Calculated for $C_{18}H_{18}O_5$ $M^{+\bullet}$, 314.1154.
Optical rotation $[\alpha]_D^{19}$ +50.0 (*c* 1.25, $CHCl_3$).

Methyl (1*S*,2*R*,3*S*,5*S*,6*R*,8*R*)-6-(benzoyloxy)-7-oxo-5-methyltricyclo [3.3.0.0^{2,8}]octan-3-carboxylate (169c) and Methyl (1*S*,2*R*,3*S*,5*S*,6*S*,8*R*)-6-(benzoyloxy)-7-oxo-5-methyltricyclo [3.3.0.0^{2,8}]octan-3-carboxylate (169d).



160b **169c** **169d**

A solution of ester **160b** (200 mg, 0.64 mmol) and acetophenone (0.19 ml, 1.60 mmol, 2.5 eq) in acetone (128 ml) was transferred into a Pyrex™ vessel and deoxygenated then lowered into a bath containing a cooled (5°C) solution of sodium bromide (750 g) and lead(II) nitrate (8 g) in water (1000 ml). A Philips 125 W HPL-N lamp was attached outside this system and parallel to the reaction vessel. The reaction mixture was irradiated for 71 h then concentrated under reduced pressure to give a yellowish oil (416 mg) that was subjected to column chromatography (silica, 1:4 v/v ethyl acetate/hexane) to afford two fractions, A and B.

Concentration of fraction A (R_f = 0.5 in 1:2 v/v ethyl acetate/hexane) gave a clear, colourless oil that was subjected to further column chromatography (silica, 1:9 v/v ethyl acetate/dichloromethane). Concentration of the appropriate fractions (R_f = 0.7 in 1:9 v/v ethyl acetate/dichloromethane) then gave diquinane **169c** (45 mg, 22%) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07-8.02 (complex m, 2H), 7.62-7.55 (complex m, 1H), 7.48-7.42 (complex m, 2H), 4.94 (s, 1H), 3.75 (s, 3H), 2.84 (ddd, J = 11.1, 6.7 and 1.3 Hz, 1H), 2.62 (ddd, J = 6.2, 5.1 and 1.0, 1H), 2.46 (ddt, J = 10.0, 6.2 and 1.3 Hz, 1H), 2.35 (dd, J = 12.6 and 11.1 Hz, 1H), 2.33 (ddd, J = 10.0, 5.1 and 1.4 Hz, 1H), 2.19 (ddd, J = 12.6, 6.7 and 1.0 Hz, 1H), 1.33 (s, 3H);
^{13}C NMR (75 MHz, $CDCl_3$): δ 209.2 (C), 174.1 (C), 165.5 (C), 133.4 (CH), 129.9 (CH), 129.2 (C), 128.5 (CH), 82.7 (CH), 52.3 (CH_3), 49.7 (CH_2), 49.4 (C), 43.8 (CH), 40.4 (CH), 38.1 (CH), 35.8 (CH), 18.4 (CH_3);
IR ν_{max} (KBr) 2954, 2933, 1734, 1601, 1452, 1436, 1316, 1266, 1203, 1178, 1106, 1097, 1070, 1026, 939, 710 cm^{-1};
MS (EI, 70 eV) *m/z*: 314 ($M^{+\cdot}$, 4%), 283 [$(M\text{-}CH_3O\cdot)^+$, 8], 164 (31), 106 (53), 105 (100), 93 (41), 77 (88), 51 (26);

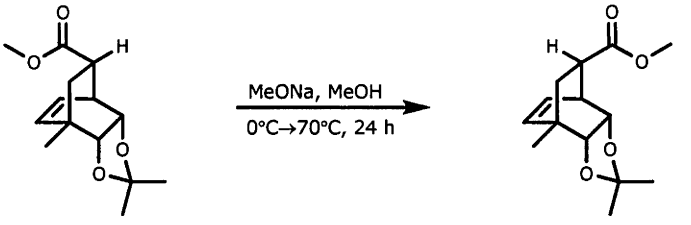
HREIMS Found: $M^{+\bullet}$, 314.1155. Calculated for $C_{18}H_{18}O_5$ $M^{+\bullet}$, 314.1154.

Optical rotation $[\alpha]_D^{19}$ +123.4 (*c* 0.5, $CHCl_3$).

Concentration of fraction B (R_f = 0.4 in 1:2 v/v ethyl acetate/hexane) gave diquinane **169d** (96 mg, 48%) as a white, crystalline solid, m.p. 102-103°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.08-8.03 (complex m, 2H), 7.62-7.56 (complex m, 1H), 7.49-7.42 (complex m, 2H), 5.38 (t, *J* = 1.2 Hz, 1H), 3.74 (s, 3H), 2.85 (ddd, *J* = 10.7, 6.9 and 1.3 Hz, 1H), 2.46 (ddd, *J* = 9.8, 5.9 and 1.3 Hz, 1H), 2.41 (dd, *J* = 5.9 and 5.4 Hz, 1H), 2.39 (ddd, *J* = 12.8, 6.9 and 1.0 Hz, 1H), 2.16 (ddt, *J* = 9.8, 5.4 and 1.0 Hz, 1H), 2.09 (ddd, *J* = 12.8, 10.7 and 1.2 Hz, 1H), 1.50 (s, 3H);
^{13}C NMR (125 MHz, $CDCl_3$): δ 205.7 (C), 174.2 (C), 165.3 (C), 133.5 (CH), 129.9 (CH), 129.1 (C), 128.5 (CH), 81.5 (CH), 52.3 (CH_3), 48.7 (C), 44.6 (CH_2), 43.6 (CH), 34.7 (CH), 31.9 (CH), 31.8 (CH), 23.4 (CH_3);
IR ν_{max} (KBr) 2957, 2928, 1738, 1729, 1601, 1452, 1435, 1330, 1294, 1269, 1248, 1203, 1177, 1110, 1072, 1051, 1026, 998, 954, 710 cm^{-1};
MS (EI, 70 eV) *m/z*: 314 ($M^{+\bullet}$, 38%), 106 (42), 105 (100), 93 (29), 77 (82), 51 (23);
HREIMS Found: $M^{+\bullet}$, 314.1154. Calculated for $C_{18}H_{18}O_5$ $M^{+\bullet}$, 314.1154.
Elemental analysis Found C, 68.83; H, 5.72; $C_{18}H_{18}O_5$ requires C, 68.78; H, 5.77%;
Optical rotation $[\alpha]_D^{20}$ -44.6 (*c* 0.5, $CHCl_3$).

(3a*S*,4*S*,7*S*,7a*R*,9*R*)-Methyl 3a,4,7,7a-tetrahydro-2,2,7-trimethyl-4,7-ethano-1,3-benzodioxol-9-carboxylate (157a).



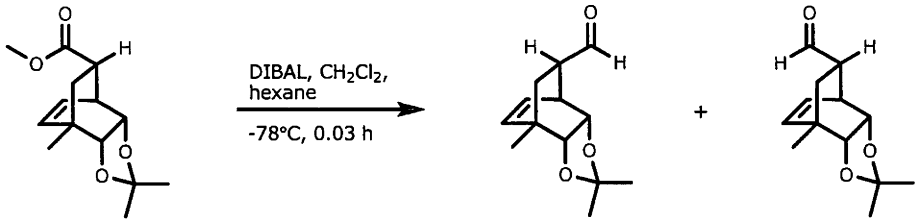
157b **157a**

A solution of ester **157b** (368 mg, 1.46 mmol) in methanol (27 ml) was cooled to 0°C then sodium methoxide [generated from sodium hydride (175 mg of a 60% dispersion in mineral oil, 4.38 mmol, 3 eq that had been washed with hexane and dried under vacuum) and methanol (18 ml)] was added. After 0.08 h the cooling bath was removed and the reaction mixture heated to 70°C for 24 h then allowed to cool to room temperature and quenched with ammonium chloride (20 ml of a saturated aq. solution). The separated aqueous phase was extracted with dichloromethane (3 x 20 ml) then the combined organic phases were washed with brine (1 x 10 ml) before being dried (magnesium sulfate), filtered and concentrated under reduced pressure to yield a colourless oil. Subjection of this material to column chromatography (silica, 1:7:12 v/v/v MeOH/ethyl acetate/hexane) afforded two fractions, A and B.

Concentration of fraction A (R_f = 0.8 in 1:7:12 v/v/v MeOH/ethyl acetate/ hexane) gave ester **157a** (62 mg, 17%) as a clear, colourless oil that was identical, in all respects, with an authentic sample. This material was used in the next step.

Concentration of fraction B (R_f = 0.8 in 1:7:12 v/v/v MeOH/ethyl acetate/ hexane) afforded ester **157b** (196 mg, 53% recovery) as a clear, colourless oil that could be resubjected to epimerisation following the above method.

(3a*S*,4*S*,7*S*,7a*R*,9*R*)-3a,4,7,7a-Tetrahydro-2,2,7-trimethyl-4,7-ethano-1,3-benzodioxol-9-carbaldehyde (171a) and (3a*S*,4*S*,7*S*,7a*R*,9*S*)-3a,4,7,7a-Tetrahydro-2,2,7-trimethyl-4,7-ethano-1,3-benzodioxol-9-carbaldehyde (171b).



157b **171a** **171b**

A solution of ester **157b** (100 mg, 0.40 mmol) in dichloromethane (10 ml) was cooled to -78°C then DIBAL (0.48 ml of a 1 M solution in hexane, 0.48 mmol, 1.2 eq) was added dropwise then the reaction mixture was stirred at -78°C for 0.03 h, quenched with potassium sodium tartrate (5 ml of a saturated solution), warmed to 18°C and stirred at this temperature for 5 h. The separated aqueous phase was extracted with dichloromethane (3 x 10 ml) then the combined organic phases were washed with brine (1 x 5 ml) before being dried (magnesium sulfate), filtered and concentrated under reduced pressure to give a clear, colourless oil. Subjection of this material to column chromatography (silica, 1:4 → 1:1 v/v ethyl/acetate/hexane) afforded two fractions, A and B.

Concentration of fraction A (R_f = 0.4 in 1:4 v/v ethyl acetate/hexane) gave aldehyde **171a** (4 mg, 5%) as a white, crystalline solid. This material was identical, in all respects, with an authentic sample.

Concentration of fraction B (R_f = 0.3 in 1:4 v/v ethyl acetate/hexane) afforded compound **171b** (58 mg, 65%) as a clear, colourless oil.

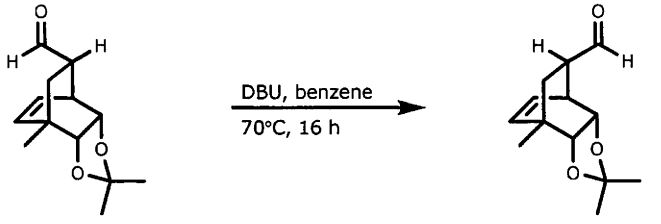
^{1}H NMR (300 MHz, $CDCl_3$): δ 9.49 (d, J = 1.1 Hz, 1H), 5.95-5.86 (complex m, 2H), 4.32 (ddd, J = 7.2, 3.3 and 1.0 Hz, 1H), 3.89 (dd, J = 7.2 and 1.0 Hz, 1H), 3.25-3.20 (complex m, 1H), 2.44 (dddd, J = 9.9, 4.7, 2.2 and 1.0 Hz, 1H), 1.64 (dd, J = 13.6 and 4.7 Hz, 1H), 1.31 (dd, J = 13.6 and 9.9 Hz, 1H), 1.30 (s, 3H), 1.28 (s, 3H), 1.27 (s, 3H);
^{13}C NMR (75 MHz, $CDCl_3$): δ 201.9 (CH), 137.9 (CH), 127.1 (CH), 108.7 (C), 83.1 (CH), 79.0 (CH), 48.0 (CH), 38.4 (C), 35.9 (CH), 29.6 (CH_2), 25.4 (CH_3), 25.0 (CH_3), 21.5 (CH_3);
IR ν_{max} (KBr) 2975, 2954, 2932, 2873, 1726, 1458, 1374, 1277, 1251, 1209, 1166, 1121, 1068, 1023, 884, 728 cm^{-1};

MS (EI, 70 eV) *m/z*: 222 ($M^{+\bullet}$, 1%), 207 [$(M\text{-}CH_3\bullet)^+$, 16], 135 (79), 117 (52), 100 (51), 93 (49), 91 (63), 85 (46), 43 (100);

HREIMS Found: $(M\text{-}CH_3\bullet)^+$, 207.1026. Calculated for $C_{13}H_{18}O_3$ $(M\text{-}CH_3\bullet)^+$, 207.1021.

Optical rotation $[\alpha]_D^{20}$ +15.3 (*c* 1.15, $CHCl_3$).

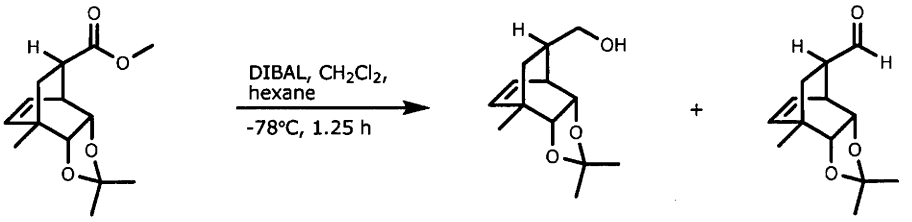
(3a*S*,4*S*,7*S*,7a*R*,9*R*)-3a,4,7,7a-Tetrahydro-2,2,7-trimethyl-4,7-ethano-1,3-benzodioxol-9-carbaldehyde (171a).



171b **171a**

DBU (26 µl, 171 µmol, 1 eq) was added to a magnetically stirred solution of aldehyde **171b** (38 mg, 171 µmol) in benzene (1 ml) and the resulting mixture heated at 70°C for 16 h, then cooled to 18°C and diluted with dichloromethane (4 ml) and washed successively with hydrochloric acid (1 x 2 ml of a 2 M aq. solution), sodium hydrogen carbonate (1 x 2 ml of a saturated aq. solution) and brine (1 x 2 ml), then dried (magnesium sulfate), filtered and concentrated under reduced pressure. ^{1}H NMR analysis of the resulting yellow oil (33 mg) established that this was comprised of a *ca.* 1:4.8 mixture of aldehydes **171a** and **171b**.

(3a*S*,4*S*,7*S*,7a*R*,9*R*)-3a,4,7,7a-Tetrahydro-2,2,7-trimethyl-4,7-ethano-1,3-benzodioxol-9-ol (170) and (3a*S*,4*S*,7*S*,7a*R*,9*R*)-3a,4,7,7a-Tetrahydro-2,2,7-trimethyl-4,7-ethano-1,3-benzodioxol-9-carbaldehyde (171a).



157a **170** **171a**

A solution of ester **157a** (50 mg, 198 μmol) in dichloromethane (5.20 ml) was cooled to -78°C then DIBAL (0.34 ml of a 1 M solution in hexane, 340 μmol, 1.7 eq) was added dropwise. The resulting reaction mixture was stirred at -78°C for 1.25 h then quenched with potassium sodium tartrate (2 ml of a saturated aq. solution), warmed to 18°C and stirred at this temperature for 15 h. The separated aqueous layer was extracted with dichloromethane (3 x 2 ml) and the combined organic phases were dried (magnesium sulfate), filtered and concentrated under reduced pressure to yield a colourless oil (46 mg). Subjection of this material to column chromatography (silica, 1:4 v/v ethyl acetate/hexane) afforded two fractions, A and B.

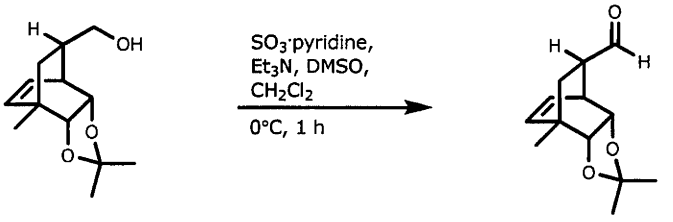
Concentration of fraction A (R_f = 0.4 in 1:4 v/v ethyl acetate/hexane) gave aldehyde **171a** (13 mg, 30%) as a white, crystalline solid, m.p. 59-62°C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.77 (s, 1H), 6.16 (dd, J = 8.1 and 6.8 Hz, 1H), 5.88 (d, J = 8.1 Hz, 1H), 4.05 (ddd, J = 7.2, 3.2 and 1.0 Hz, 1H), 3.78 (dd, J = 7.2 and 1.0 Hz, 1H), 3.29-3.27 (complex m, 1H), 2.47 (ddd, J = 11.2, 5.4 and 2.9 Hz, 1H), 1.70 (dd, J = 13.6 and 5.4 Hz, 1H), 1.29 (s, 3H), 1.27 (s, 3H), 1.21 (s, 3H), 1.20 (dd, J = 13.6 and 11.2 Hz, 1H);
^{13}C NMR (125 MHz, $CDCl_3$): δ 202.4 (CH), 137.5 (CH), 129.5 (CH), 108.1 (C), 82.5 (CH), 75.9 (CH), 49.5 (CH), 38.8 (C), 35.4 (CH), 28.1 (CH_2), 25.4 (CH_3), 24.9 (CH_3), 21.6 (CH_3);
IR ν_{max} (KBr) 2975, 2955, 2934, 2872, 1722, 1458, 1373, 1264, 1254, 1208, 1165, 1135, 1071, 1058, 971, 884, 824, 729, 699 cm^{-1};
MS (EI, 70 eV) *m/z*: 223 [$(M+H)^+$, 15%], 222 ($M^{+\cdot}$, 5), 207 [$(M-CH_3\cdot)^+$, 46], 164 (63), 135 (98), 117 (65), 93 (67), 92 (100), 91 (63), 43 (75);
HREIMS Found: $M^{+\cdot}$, 222.1253. Calculated for $C_{13}H_{18}O_3$ $M^{+\cdot}$, 222.1256.
Elemental analysis Found: C, 70.05; H, 8.00; $C_{13}H_{18}O_3$ requires: C, 70.25; H, 8.16%;
Optical rotation $[\alpha]_D^{19}$ -31.0 (*c* 1, $CHCl_3$).

Concentration of fraction B (R_f = 0.1 in 1:4 v/v ethyl acetate/hexane) afforded alcohol **170** (25 mg, 57%) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.16 (dd, J = 8.2 and 6.9 Hz, 1H), 5.80 (d, J = 8.2 Hz, 1H), 4.39 (dd, J = 7.3 and 3.2 Hz, 1H), 3.79 (d, J = 7.3 Hz, 1H), 3.64-3.47 (complex m, 2H), 2.96-2.92 (complex m, 1H), 1.85-1.74 (complex m, 2H), 1.35 (dd, J = 13.3 and 11.1 Hz, 1H), 1.31 (s, 3H), 1.26 (s, 3H), 1.22 (s, 3H), 0.69 (dd, J = 13.3 and 5.9 Hz, 1H);
^{13}C NMR (75 MHz, $CDCl_3$): δ 135.6 (CH), 131.9 (CH), 107.7 (C), 83.1 (CH), 75.6 (CH), 65.0 (CH_2), 38.6 (CH), 38.4 (C), 35.9 (CH), 33.1 (CH_2), 25.5 (CH_3), 24.9 (CH_3), 21.7 (CH_3);
IR ν_{max} (KBr) 3417, 3044, 2970, 2933, 2869, 1457, 1374, 1269, 1246, 1207, 1165, 1075, 1058, 1028, 885, 730, 705, 691, 513 cm^{-1};
MS (EI, 70 eV) *m/z*: 209 [$(M\text{-}CH_3\cdot)^+$, 25%], 166 (60), 135 (100), 93 (63);
HREIMS Found: $(M\text{-}CH_3\cdot)^+$, 209.1179. Calculated for $C_{13}H_{18}O_3$ $(M\text{-}CH_3\cdot)^+$, 209.1178.
Optical rotation $[\alpha]_D^{18}$ -17.3 (*c* 0.9, $CHCl_3$).

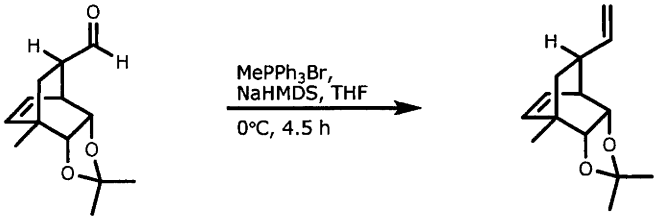
(3a*S*,4*S*,7*S*,7a*R*,9*R*)-3a,4,7,7a-Tetrahydro-2,2,7-trimethyl-4,7-ethano-1,3-benzodioxol-9-carbaldehyde (171a).



170 **171a**

A magnetically stirred solution of alcohol **170** (980 mg, 4.37 mmol) in dichloromethane/DMSO (62 ml of a 1:1 v/v mixture) was cooled to 0°C then treated with triethylamine (3 ml, 21.85 mmol, 5 eq) and SO_3·pyridine complex (2.09 g, 13.11 mmol, 3 eq). The ensuing mixture was stirred at 0°C for 1 h then diluted with diethyl ether (50 ml), washed with hydrochloric acid (1 x 10 ml of a 1 M aq. solution), sodium hydrogen carbonate (1 x 10 ml of a saturated aq. solution) and brine (1 x 10 ml) before being dried (magnesium sulfate), filtered and concentrated under reduced pressure. The resulting light-orange oil (922 mg) was subjected to column chromatography (silica, 1:5:14 v/v/v MeOH/ethyl acetate/hexane) and then giving, after concentration of the appropriate fractions (R_f = 0.4 in 1:4 v/v ethyl acetate/hexane), aldehyde **171a** (497 mg, 51%) as a light-yellow oil that was identical, in all respects, with an authentic sample.

(3a*S*,4*S*,7*S*,7a*R*,9*S*)-3a,4,7,7a-Tetrahydro-2,2,7-trimethyl-9-vinyl-4,7-ethano-1,3-benzodioxole (172).



171a **172**

$MePPh_3Br$ was dried at 100°C for 15 h then cooled and stored under nitrogen. Some of the dried material (2.05 g, 5.73 mmol, 3.0 eq) was mixed with THF (19.1 ml) then cooled to 0°C and treated dropwise with NaHMDS (4.58 ml of a 1 M solution in THF, 4.58 mmol, 2.4 eq). The mixture was stirred at 0°C for 2.5 h and the resulting bright yellow reaction mixture treated dropwise with a solution of aldehyde **171a** (424 mg, 1.91 mmol) in THF (8.50 ml). Stirring was continued at 0°C for 2 h then the reaction mixture was quenched with ammonium chloride (10 ml of a saturated aq. solution) and diluted with dichloromethane (10 ml). The separated aqueous phase was extracted with dichloromethane (3 x 20 ml) then the combined organic phases were washed with brine (1 x 10 ml) before being dried (magnesium sulfate), filtered and concentrated under reduced pressure. The thus obtained orange oil was subjected to column chromatography (silica, 1:9 v/v ethyl acetate/hexane) and concentration of the appropriate fractions then gave olefin **172** (253 mg, 60%) as a clear, colourless oil.

R_f = 0.5 in 1:9 v/v ethyl acetate/hexane;

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.17 (ddd, J = 7.8, 6.3 and 1.0 Hz, 1H), 5.83 (ddd, J = 17.2, 10.3 and 6.9 Hz, 1H), 5.79 (dd, J = 7.8 and 1.0 Hz, 1H), 5.11-5.01 (complex m, 2H), 4.36 (ddd, J = 7.4, 3.3 and 1.0 Hz, 1H), 3.81 (dd, J = 7.4 and 1.0 Hz, 1H), 2.80-2.74 (complex m, 1H), 2.29-2.18 (complex m, 1H), 1.39 (dd, J = 13.4 and 11.0 Hz, 1H), 1.32 (s, 3H), 1.26 (s, 3H), 1.24 (s, 3H), 1.01 (dd, J = 13.4 and 5.8 Hz, 1H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 141.0 (CH), 135.4 (CH), 131.9 (CH), 114.6 (CH_2), 107.6 (C), 83.3 (CH), 75.9 (CH), 40.8 (CH), 39.4 (CH), 38.7 (C), 34.6 (CH_2), 25.5 (CH_3), 24.9 (CH_3), 21.8 (CH_3);

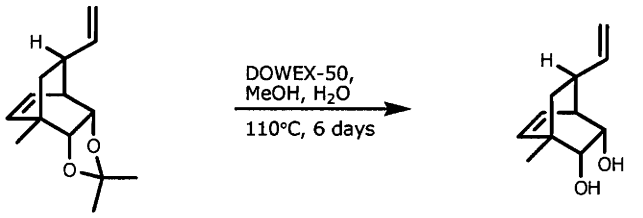
IR ν_{max} (KBr) 3045, 2976, 2952, 2937, 2903, 2869, 1638, 1457, 1378, 1371, 1262, 1233, 1207, 1165, 1069, 1056, 995, 912, 885, 861, 809, 729, 707 cm^{-1};

MS (EI, 70 eV) *m/z*: 220 ($M^{+\cdot}$, 18%), 219 [$(M\text{-}H\cdot)^+$, 38], 205 [$(M\text{-}CH_3\cdot)^+$, 11], 163 (68), 105 (64), 57 (100), 43 (46);

HREIMS Found: $(M\text{-}H\cdot)^+$, 219.1382. Calculated for $C_{14}H_{20}O_2$ $(M\text{-}H\cdot)^+$, 219.1385.

Optical rotation $[\alpha]_D^{18}$ -45.3 (*c* 0.55, $CHCl_3$).

(1*S*,2*R*,3*S*,4*S*,5*S*)-1-Methyl-5-vinylbicyclo[2.2.2]oct-7-ene-2,3-diol (173).



172 **173**

DOWEX-50 was activated by washing it twice with methanol, twice with hydrochloric acid (2 M aq. solution) and, finally, twice with water. The resulting activated resin (269 mg) was added to a solution of acetonide **172** (269 mg, 1.22 mmol) in MeOH/water (6 ml of a 5:1 v/v mixture) and the suspension so generated was heated to 110°C. After six days the mixture was cooled, filtered and DOWEX washed three times with methanol. The combined filtrates were concentrated under reduced pressure. The resin was washed twice with dichloromethane and the filtrate added to the concentrated residue, which was then washed with sodium chloride (1 x 10 ml of a 1.5 M aq. solution). The separated aqueous phase was extracted with dichloromethane (3 x 10 ml) then the combined organic phases were dried (magnesium sulfate), filtered and concentrated under reduced pressure. The thus obtained orange oil (201 mg) was subjected to column chromatography (silica, 1:4 -> 1:1 v/v ethyl acetate/hexane) and concentration of the appropriate fractions then gave diol **173** (146 mg, 66%) as a clear, colourless oil.

R_f = 0.5 in 1:1 v/v ethyl acetate/hexane;

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.32 (ddd, J = 8.1, 7.0 and 0.8 Hz, 1H), 5.90 (dd, J = 8.1 and 0.8 Hz, 1H), 5.82 (ddd, J = 17.0, 10.3 and 6.7 Hz, 1H), 5.10-5.01 (complex m, 2H), 4.05 (ddd, J = 7.6, 2.5 and 0.8 Hz, 1H), 3.44 (dd, J = 7.6 and 0.8 Hz, 1H), 2.80 (broad s, 2H), 2.67-2.62 (complex m, 1H), 2.20-2.09 (complex m, 1H), 1.38 (dd, J = 13.5 and 11.2 Hz, 1H), 1.23 (s, 3H), 1.06 (dd, J = 13.5 and 6.2 Hz, 1H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 140.8 (CH), 136.6 (CH), 133.4 (CH), 114.9 (CH_2), 75.6 (CH), 67.9 (CH), 43.8 (CH), 40.2 (C), 40.0 (CH), 35.3 (CH_2), 21.6 (CH_3);

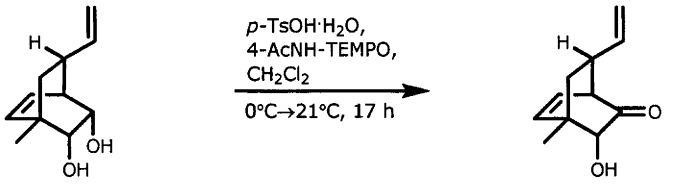
IR ν_{max} (KBr) 3374, 2928, 2869, 1637, 1457, 1403, 1372, 1065, 1031, 994, 959, 910, 726, 703, 601 cm^{-1};

MS (EI, 70 eV) *m/z*: 180 ($M^{+\cdot}$, 5%), 120 (97), 105 (100), 92 (72), 91 (53);

HREIMS Found: $M^{+\cdot}$, 180.1144. Calculated for $C_{11}H_{16}O_2$ $M^{+\cdot}$, 180.1150.

Optical rotation $[\alpha]_D^{19}$ -76.1 (*c* 1, $CHCl_3$).

(1*S*,3*R*,4*S*,6*S*)-3-Hydroxy-4-methyl-6-vinylbicyclo[2.2.2]oct-7-ene-2-one (174).



173 **174**

A solution of diol **173** (146 mg, 0.81 mmol) in dichloromethane (19.50 ml) was cooled to 0°C then *p*-TsOH·H_2O (339 mg, 1.78 mmol, 2.2 eq) was added followed by 4-AcNH-TEMPO (380 mg, 1.78 mmol, 2.2 eq) and the mixture thus obtained was allowed to reach 21°C. After 17 h at the latter temperature, the reaction mixture was quenched with sodium hydrogen carbonate (10 ml of a saturated aq. solution) and extracted with dichloromethane (3 x 20 ml). The combined organic extracts were washed with brine (1 x 10 ml) before being dried (magnesium sulfate), filtered and concentrated under reduced pressure. The resulting orange semi-solid (533 mg) was subjected to column chromatography (silica, 1:4 v/v ethyl acetate/hexane) and concentration of the appropriate fractions then gave compound **174** (118 mg, 81%) as a clear, colourless oil.

R_f = 0.3 in 1:4 v/v ethyl acetate/hexane;

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.19 (dd, J = 7.7 and 6.6 Hz, 1H), 6.11 (d, J = 7.7 Hz, 1H), 5.68 (ddd, J = 17.0, 10.3 and 7.3 Hz, 1H), 5.10-4.98 (complex m, 2H), 3.37 (s, 1H), 3.20 (dd, J = 6.6 and 2.2 Hz, 1H), 2.73 (broad s, 1H), 2.61-2.50 (complex m, 1H), 1.80 (dd, J = 13.4 and 11.7 Hz, 1H), 1.43 (dd, J = 13.4 and 4.7 Hz, 1H), 1.31 (s, 3H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 211.6 (C), 140.7 (CH), 140.5 (CH), 126.9 (CH), 115.1 (CH_2), 75.1 (CH), 52.7 (CH), 42.2 (C), 39.0 (CH), 37.9 (CH_2), 20.0 (CH_3);

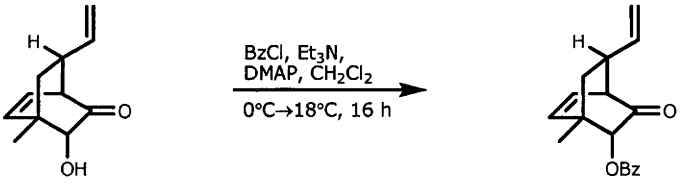
IR ν_{max} (KBr) 3448, 2970, 2954, 2931, 2869, 1725, 1639, 1457, 1115, 1068, 990, 915, 776, 709 cm^{-1};

MS (EI, 70 eV) *m/z*: 178 ($M^{+\bullet}$, 8%), 106 (72), 105 (100), 91 (71), 79 (70), 43 (73), 39 (64), 32 (67);

HREIMS Found: $M^{+\bullet}$, 178.0986. Calculated for $C_{11}H_{14}O_2$ $M^{+\bullet}$, 178.0994.

Optical rotation $[\alpha]_D^{22}$ +346.5 (*c* 0.65, $CHCl_3$).

(1*S*,2*R*,4*S*,5*S*)-1-Methyl-3-oxo-5-vinylbicyclo[2.2.2]oct-7-en-2-yl benzoate (175).



174 **175**

A magnetically stirred solution of acyloin **174** (118 mg, 0.66 mmol) in dichloromethane (21 ml) was cooled to 0°C then treated with triethylamine (0.46 ml, 3.30 mmol, 5 eq), DMAP (9 mg, 0.07 mmol, 10 mol%) and benzoyl chloride (0.15 ml, 1.32 mmol, 2 eq). The ensuing mixture was allowed to warm to 18°C and after 16 h it was quenched with sodium hydrogen carbonate (10 ml of a saturated aq. solution). The separated aqueous phase was extracted with dichloromethane (3 x 20 ml) then the combined organic extracts were washed with brine (1 x 10 ml) before being dried (magnesium sulfate), filtered and concentrated under reduced pressure. The yellow semi-solid (301 mg) thus obtained was subjected to column chromatography (silica, 1:4 v/v ethyl acetate/hexane) and concentration of the appropriate fractions gave adduct **175** (199 mg, 0.71 mmol, quant.) as a white oil.

R_f = 0.6 in 1:4 v/v ethyl acetate/hexane;

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.02-7.98 (complex m, 2H), 7.59-7.52 (complex m, 1H), 7.46-7.39 (complex m, 2H), 6.32 (dd, J = 7.8 and 6.7 Hz, 1H), 6.20 (d, J = 7.8 Hz, 1H), 5.76 (ddd, J = 17.2, 10.3 and 7.4 Hz, 1H), 5.16-5.05 (complex m, 2H), 5.08 (s, 1H), 3.26 (ddd, J = 6.7, 2.9 and 1.1 Hz, 1H), 2.67-2.56 (complex m, 1H), 1.89 (dd, J = 13.6 and 11.5 Hz, 1H), 1.62 (dd, J = 13.6 and 4.9 Hz, 1H), 1.22 (s, 3H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 205.3 (C), 166.1 (C), 140.0 (CH), 139.8 (CH), 133.2 (CH), 129.9 (CH), 129.4 (C), 128.3 (CH), 127.6 (CH), 115.6 (CH_2), 74.5 (CH), 53.5 (CH), 41.3 (C), 39.5 (CH), 37.5 (CH_2), 20.1 (CH_3);

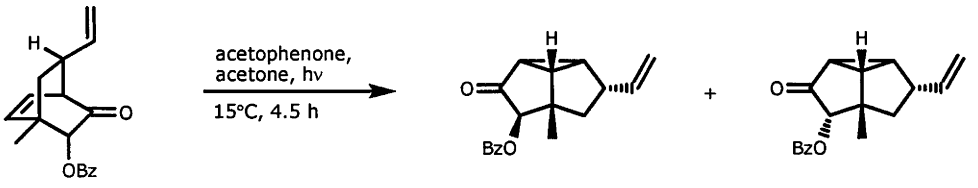
IR ν_{max} (KBr) 2965, 2925, 2869, 2853, 1741, 1724, 1451, 1328, 1266, 1254, 1177, 1111, 1070, 1029, 921, 708 cm^{-1};

MS (EI, 70 eV) *m/z*: 282 ($M^{+\bullet}$, 21%), 160 (37), 132 (62), 120 (41), 106 (76), 105 (100), 91 (30), 77 (89), 51 (43);

HREIMS Found: $M^{+\bullet}$, 282.1255. Calculated for $C_{18}H_{18}O_3$ $M^{+\bullet}$, 282.1256.

Optical rotation $[\alpha]_D^{20}$ +255.9 (*c* 1, $CHCl_3$).

(1*S*,2*R*,4*R*,5*S*,7*S*,8*R*)-4-(Benzoyloxy)-5-methyl-7-vinyltricyclo[3.3.0.0^{2,8}] octan-3-one (176a) and (1*S*,2*R*,4*S*,5*S*,7*S*,8*R*)-4-(Benzoyloxy)-5-methyl-7-vinyltricyclo[3.3.0.0^{2,8}]octan-3-one (176b).



175 **176a** **176b**

A magnetically stirred and deoxygenated solution of acyloin **175** (186 mg, 0.66 mmol) and acetophenone (0.23 ml, 1.98 mmol, 3 eq) in acetone (300 ml) was placed in a quartex immersion well photoreactor (Ace Glass Inc., 500 ml) equipped with a Pyrex filter. The mixture was subjected to irradiation with a Hanovia 450W medium pressure quartz mercury-vapour lamp. After 4.67 h the reaction mixture was removed from the photoreactor and concentrated under reduced pressure to give a yellowish oil (459 mg) that was subjected to column chromatography (silica, 1:4 v/v ethyl acetate/hexane) to afford two fractions, A and B.

Concentration of fraction A yielded a mixture of acetophenone and diquinane **176a** (49 mg) as a clear, colourless oil. Resubjection of the material to flash chromatography (silica, 1:9 v/v ethyl acetate/hexane) and concentration of the appropriate fractions then gave compound **176a** (29 mg, 15%) as a clear, colourless oil.

R_f = 0.5 in 1:4 v/v ethyl acetate/hexane

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06-8.02 (complex m, 2H), 7.60-7.54 (complex m, 1H), 7.47-7.40 (complex m, 2H), 5.82 (ddd, J = 17.3, 10.4 and 5.6 Hz, 1H), 5.19-5.02 (complex m, 2H), 5.08 (broad s, 1H), 3.46-3.35 (complex m, 1H), 2.61 (ddd, J = 6.0, 5.1 and 1.0 Hz, 1H), 2.43 (dd, J = 13.5 and 11.0 Hz, 1H), 2.33 (m, 1H), 2.23 (m, 1H), 1.89 (dt, J = 13.5 and 1.4 Hz, 1H), 1.28 (s, 3H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 210.9 (C), 165.6 (C), 139.5 (CH), 133.2 (CH), 129.9 (CH), 129.5 (C), 128.4 (CH), 115.8 (CH_2), 83.5 (CH), 49.9 (C), 49.8 (CH_2), 43.0 (CH), 42.0 (CH), 39.8 (CH), 38.4 (CH), 19.3 (CH_3);

IR ν_{max} (KBr) 2970, 2935, 2874, 1722, 1451, 1266 (broad), 1177, 1107, 1094, 1069, 1026, 990, 957, 915, 852, 709, 668 cm^{-1};

MS (EI, 70 eV) *m/z*: 282 ($M^{+\cdot}$, 2%), 160 (25), 132 (45), 106 (55), 105 (71), 91 (37), 77 (100);

HREIMS Found: $M^{+\cdot}$, 282.1260. Calculated for $C_{18}H_{18}O_3$ $M^{+\cdot}$, 282.1256.

Optical rotation $[\alpha]_D^{19}$ +139.1 (*c* 0.9, $CHCl_3$).

Concentraction of fraction B gave diquinane **176b** (30 mg, 17%) as a clear, colourless oil.

R_f = 0.4 in 1:4 v/v ethyl acetate/hexane

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07-8.03 (complex m, 2H), 7.61-7.55 (complex m, 1H), 7.48-7.42 (complex m, 2H), 5.80 (ddd, J = 17.0, 10.3 and 7.0 Hz, 1H), 5.44 (t, J = 1.5 Hz, 1H), 5.11 (dt, J = 17.0 and 1.5 Hz, 1H), 5.01 (dt, 10.3 and 1.5 Hz, 1H), 3.45-3.35 (complex m, 1H), 2.37 (dd, J = 5.9 and 4.8 Hz, 1H), 2.28 (dt, J = 9.8 and 5.9 Hz, 1H), 2.12 (ddd, J = 14.0, 11.0 and 1.5 Hz, 1H), 2.05-1.98 (complex m, 2H), 1.45 (s, 3H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 207.1 (C), 165.4 (C), 139.2 (CH), 133.3 (CH), 129.9 (CH), 129.3 (C), 128.4 (CH), 115.3 (CH_2), 82.1 (CH), 49.3 (C), 44.2 (CH), 43.5 (CH_2), 36.4 (CH), 35.8 (CH), 32.6 (CH), 24.3 (CH_3);

IR ν_{max} (KBr) 2959, 1739, 1724, 1452, 1331, 1269, 1248, 1177, 1113, 1097, 1071, 1026, 1000, 916, 850, 709 cm^{-1};

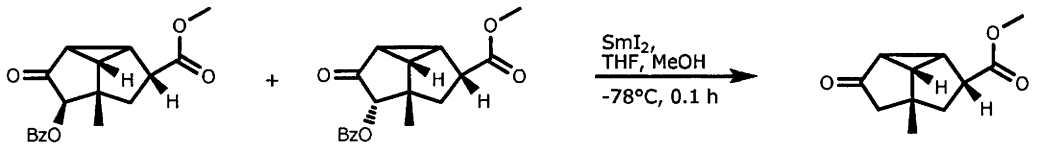
MS (EI, 70 eV) *m/z*: 282 ($M^{+\bullet}$, 11%), 160 (37), 132 (49), 106 (52), 105 (100), 77 (69);

HREIMS Found: $M^{+\bullet}$, 282.1256. Calculated for $C_{18}H_{18}O_3$ $M^{+\bullet}$, 282.1256.

Optical rotation $[\alpha]_D^{18}$ +60.2 (*c* 0.6, $CHCl_3$).

5.4 Experimental procedures associated with work described in Chapter 4

Methyl (1*S*,2*R*,3*R*,5*R*,8*R*)-7-oxo-5-methyltricyclo[3.3.0.0^{2,8}]octan-3-carboxylate (188).



169a **169b** **188**

A magnetically stirred solution of a 1:10 mixture of diquinanes **169a** and **169b** (712 mg, 2.27 mmol) in THF/MeOH (33 ml of a 2:1 v/v mixture) was cooled to -78°C then samarium diiodide (*ca.* 22 ml of a 0.1 M solution in THF, 2.2 eq) was added dropwise until the reaction mixture remained blue. This was stirred at -78°C for 0.1 h then quenched with potassium carbonate (45 ml of a saturated aq. solution) and allowed to warm to 18°C. The separated aqueous phase was extracted with diethyl ether (3 x 90 ml) then the combined organic phases were washed with brine (1 x 90 ml) before being dried (magnesium sulfate), filtered and concentrated under reduced pressure. The yellow semi-solid thus obtained was subjected to column chromatography (silica, 1:1 v/v ethyl acetate/hexane) and concentration of the appropriate fractions then gave diquinane **188** (315 mg, 71%) as a white, crystalline solid, m.p. 80-82°C.

R_f = 0.5 in 1:1 v/v ethyl acetate/hexane;

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.65 (s, 3H), 3.43 (dt, J = 7.3 and 4.4 Hz, 1H), 2.48 (dd, J = 5.9 and 5.3 Hz, 1H), 2.29-2.20 (complex m, 3H), 2.18-2.11 (complex m, 2H), 2.00 (dd, J = 9.5 and 5.3 Hz, 1H), 1.39 (s, 3H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 213.4 (C), 173.8 (C), 54.5 (CH_2), 52.0 (CH_3), 48.6 (CH_2), 46.3 (C), 44.6 (CH), 42.0 (CH), 39.5 (CH), 33.3 (CH), 25.5 (CH_3);

IR ν_{max} (KBr) 2953, 2920, 2870, 2850, 1729, 1452, 1434, 1336, 1307, 1273, 1253, 1238, 1205, 1183, 1131, 1050, 1017, 981, 884, 817 cm^{-1};

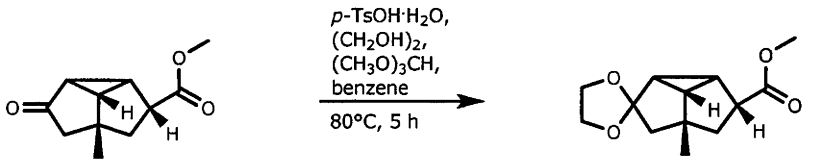
MS (EI, 70 eV) *m/z*: 194 ($M^{+\bullet}$, 84%), 152 (68), 135 (72), 108 (81), 107 (79), 93 (100), 92 (86), 91 (88), 79 (66), 77 (71);

HREIMS Found: $M^{+\bullet}$, 194.0952. Calculated for $C_{11}H_{14}O_3$ $M^{+\bullet}$, 194.0943.

Elemental analysis Found C, 68.10; H, 7.20; $C_{11}H_{14}O_3$ requires C, 68.02; H, 7.26%;

Optical rotation $[\alpha]_D^{20}$ +19.9 (*c* 1, $CHCl_3$).

Methyl (1*S*,2*R*,3*R*,5*R*,8*R*)-7,7-ethylenedioxy-5-methyltricyclo[3.3.0.0^{2,8}]-octan-3-carboxylate (189).



188 **189**

Ethylene glycol (1.17 g, 18.84 mmol, 11.7 eq), trimethyl orthoformate (342 mg, 3.22 mmol, 2 eq) and *p*-TsOH·H_2O (15 mg, 0.08 mmol, 0.05 eq) were added to a magnetically stirred solution of diquinane **188** (312 mg, 1.61 mmol) in benzene (68 ml). The resulting mixture was heated to 80°C and stirred at this temperature for 5 h. The cooled reaction mixture was quenched with sodium hydrogen carbonate (35 ml of a saturated aq. solution) and the separated aqueous phase was extracted with diethyl ether (3 x 70 ml). The combined organic extracts were washed with brine (1 x 70 ml) before being dried (magnesium sulfate), filtered and concentrated under reduced pressure. The resulting yellow oil was subjected to column chromatography (silica, 1:2 v/v ethyl acetate/hexane) and concentration of the appropriate fractions then gave diquinane **189** (259 mg, 68%) as a clear, colourless oil that solidified on standing to give a white, crystalline solid, m.p. 36-41°C.

R_f = 0.5 in 1:2 v/v ethyl acetate/hexane;

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.88-3.83 (complex m, 4H), 3.68 (split s, 3H), 3.39 (ddd, J = 12.1, 6.6 and 3.4 Hz, 1H), 2.23 (dd, J = 13.2 and 2.0 Hz, 1H), 2.20 (dd, J = 13.5 and 3.4 Hz, 1H), 2.09 (ddd, J = 13.5, 12.1 and 2.1 Hz, 1H), 1.99 (t, J = 6.6 Hz, 1H), 1.85 (dd, J = 13.2 and 1.4 Hz, 1H), 1.83-1.74 (complex m, 1H), 1.52 (dd, J = 8.5 and 6.6 Hz, 1H), 1.23 (s, 3H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 175.3 (C), 116.7 (C), 64.3 (CH_2), 63.3 (CH_2), 56.6 (CH_2), 51.4 (CH), 48.2 (C), 46.0 (CH_2), 45.3 (CH), 38.7 (CH), 32.7 (CH), 30.0 (CH), 25.8 (CH_3);

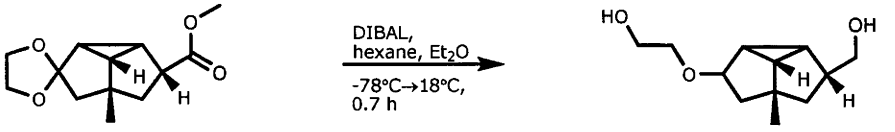
IR ν_{max} (KBr) 2952, 2928, 2886, 1734, 1453, 1433, 1371, 1343, 1323, 1252, 1213, 1172, 1121, 1083, 1054, 1028, 982, 964, 949, 926, 860, 845, 789, 776, 761 cm^{-1};

GC-MS (EI, 70 eV) *m/z*: 238 ($M^{+\cdot}$, 26%), 139 (44), 100 (32), 93 (100), 91 (38), 87 (33);

HREIMS Found: $M^{+\cdot}$, 238.1208. Calculated for $C_{13}H_{18}O_4$ $M^{+\cdot}$, 238.1205.

Optical rotation $[\alpha]_D^{19}$ -46.8 (*c* 1, $CHCl_3$).

2-[(1*S*,2*S*,3*R*,5*R*,8*R*)-3-(Hydroxymethyl)-5-methyltricyclo[3.3.0.0^{2,8}]-oct-7-yloxy]ethanol (190).

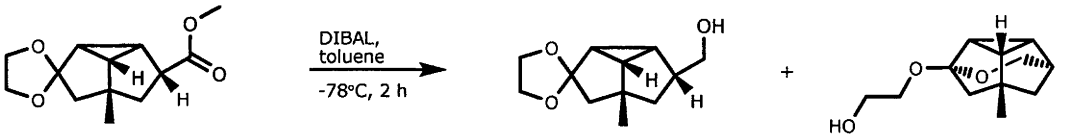


189 **190**

A magnetically stirred solution of crude diquinane **189** (21 mg, 88 μmol) in diethyl ether (1 ml) was cooled to -78°C then DIBAL (0.32 ml of a 1 M solution in hexane, 320 μmol, 3.5 eq) was added dropwise. The resulting mixture was allowed to warm to 18°C and after 0.7 h it was quenched with distilled water (1 ml). The separated aqueous phase was extracted with dichloromethane (3 x 2 ml) then the combined organic phases were washed with brine (1 x 2 ml) before being dried (magnesium sulfate), filtered and concentrated under reduced pressure. The clear, colourless oil thus obtained was subjected to column chromatography (silica, 13:7 v/v ethyl acetate/hexane) and concentration of the appropriate fractions then gave diol **190** (9 mg, 48%) as a clear, colourless oil.

R_f = 0.3 in 13:7 v/v ethyl acetate/hexane;
^{1}H NMR (500 MHz, $CDCl_3$): δ 4.46 (ddd, J = 9.4, 5.8 and 1.9 Hz, 1H), 3.89-3.69 (complex m, 4H), 3.65-3.51 (complex m, 2H), 3.01-2.87 (complex m, 1H), 2.08 (ddd, J = 13.9, 9.4 and 1.8 Hz, 1H), 2.00 (ddd, J = 13.2, 11.5 and 1.8 Hz, 1H), 1.88 (t, J = 6.6 Hz, 1H), 1.76-1.63 (complex m, 2H), 1.56-1.48 (complex m, 2H), 1.19 (s, 3H) (signals due to OH protons obscured or overlapping);
^{13}C NMR (125 MHz, $CDCl_3$): δ 82.4 (CH), 71.4 (CH_2), 64.0 (CH_2), 62.0 (CH_2), 51.6 (CH_2), 49.8 (C), 47.3 (CH_2), 43.1 (CH), 38.3 (CH), 32.9 (CH), 31.9 (CH), 26.4 (CH_3);
IR ν_{max} (KBr) 3342, 3021, 2924, 2856, 2454, 1353, 1154, 1100, 1067, 1040 cm^{-1};
MS (ESI, +ve ion mode) *m/z*: 235 [(M+Na)$^+$, 76%], 133 (100);
HRESMS Found: (M+Na)$^+$, 235.131249. Calculated for $C_{12}H_{20}O_3$ (M+Na)$^+$, 235.131014.

[(1*S*,2*S*,3*R*,5*R*,8*R*)-7,7-Ethylenedioxy-5-methyltricyclo[3.3.0.0^{2,8}]octan-3-yl]methanol (191) and 2-[(1*R*,2*R*,3*S*,4*S*,5*R*,7*R*)-7-Methyl-9-oxatetracyclo[3.3.2.0^{2,4}.0^{3,7}]oct-1-yloxy]ethanol (192).



189 **191** **192**

A magnetically stirred solution of ester **189** (71 mg, 298 μmol) in toluene (2.4 ml) was cooled to -78°C then treated, dropwise, with DIBAL (417 μl of a 1 M solution in toluene, 417 μmol, 1.4 eq). The resulting mixture was stirred at -78°C for 2 h then quenched with sodium hydrogensulfite (2.5 ml of a saturated aq. solution) and allowed to gradually reach room temperature. The separated organic phase was washed with sodium hydrogensulfite (2 x 2.5 ml of a saturated aq. solution). The pH of the combined aqueous phases was adjusted to 8 using sodium hydroxide (2 M aq. solution) and the resulting mixture then extracted with diethyl ether (3 x 5 ml). All combined organic phases were washed with distilled water (1 x 2.5 ml) then dried (magnesium sulfate), filtered and concentrated under reduced pressure. The yellow oil (53 mg) thus obtained was subjected to column chromatography (silica, 1:1 v/v ethyl acetate/hexane) and three fractions, A, B and C, were thereby obtained.

Concentration of fraction A (R_f = 0.6 in 1:1 v/v ethyl acetate/hexane) gave starting material **189*** (13 mg, 18%) as a clear, colourless oil that was identical, in all respects, with an authentic sample.

Concentration of fraction B (R_f = 0.3 in 1:1 v/v ethyl acetate/hexane) afforded alcohol **192** (8 mg, 13%) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.87 (ddd, J = 9.5, 2.7 and 0.8 Hz, 1H) 3.81-3.66 (complex m, 5H), 3.24 (dd, J = 5.8 and 5.5 Hz, 1H), 2.57-2.49 (complex m, 1H), 2.14 (dd, J = 11.3 and 2.6 Hz, 1H), 2.03 (dddd, J = 12.1, 9.2, 2.6 and 0.8 Hz, 1H), 1.85-1.72 (complex m, 3H), 1.61 (ddd, J = 8.1, 6.7 and 1.1 Hz, 1H), 1.47 (d, J = 12.1 Hz, 1H), 1.23 (s, 3H);
^{13}C NMR (75 MHz, $CDCl_3$): δ 106.0 (C), 67.6 (CH_2), 66.6 (CH_2), 62.2 (CH_2), 59.7 (CH_2), 51.9 (CH_2), 46.6 (C), 35.5 (CH), 34.6 (CH), 26.8 (CH), 26.2 (CH), 23.9 (CH_3);

* Deprotection of the ketal group occured rapidly when running NMR spectra of the compound in deuterated chloroform from which traces of acid had not been removed.

IR ν_{max} (KBr) 3436, 2949, 2925, 2868, 2453, 1376, 1358, 1343, 1326, 1308, 1243, 1232, 1214, 1185, 1170, 1152, 1110, 1089, 1041, 1022, 1005, 977, 953, 942, 892, 881, 855 cm^{-1};

MS (EI, 70 eV) *m/z*: 210 ($M^{+\bullet}$, 41%), 180 (100), 137 (42), 121 (38), 107 (51), 105 (52), 93 (65), 91 (63), 79 (54);

HREIMS Found: $M^{+\bullet}$, 210.1248. Calculated for $C_{12}H_{18}O_3$ $M^{+\bullet}$, 210.1256.

Optical rotation $[\alpha]_D^{18}$ -34.0 (*c* 0.75, $CHCl_3$).

Concentration of fraction C (R_f = 0.3 in 1:1 v/v ethyl acetate/hexane) yielded alcohol **191** (19 mg, 30%) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.07-4.00 (complex m, 1H), 3.99-3.78 (complex m, 5H), 2.99-2.86 (complex m, 1H), 2.59 (broad s, 1H), 2.21 (dd, *J* = 13.7 and 1.8 Hz, 1H), 2.00 (dd, *J* = 6.6 and 6.3 Hz, 1H), 1.99 (ddd, *J* = 13.3, 11.5 and 1.8 Hz, 1H), 1.90 (d, *J* = 13.7 Hz, 1H), 1.52-1.44 (complex m, 3H), 1.24 (s, 3H);

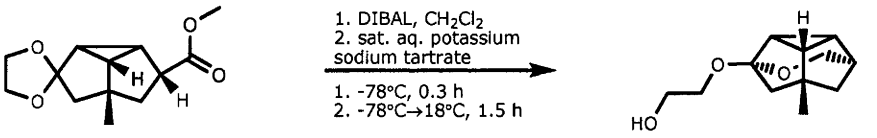
^{13}C NMR (75 MHz, $CDCl_3$): δ 118.1, 64.8, 64.2, 63.6, 57.4, 48.9, 47.2, 43.9, 37.5, 35.2, 30.8, 26.3;

IR ν_{max} (KBr) 3381, 2949, 2925, 2862, 1454, 1374, 1345, 1260, 1237, 1169, 1122, 1093, 1056, 1029, 981, 947, 919, 847, 794, 667 cm^{-1};

MS (EI) *m/z*: 210 ($M^{+\bullet}$, 17%), 180 (38), 93 (100), 91 (56), 79 (39), 43 (42);

HREIMS Found: $M^{+\bullet}$, 210.1251. Calculated for $C_{12}H_{18}O_3$ $M^{+\bullet}$, 210.1256.

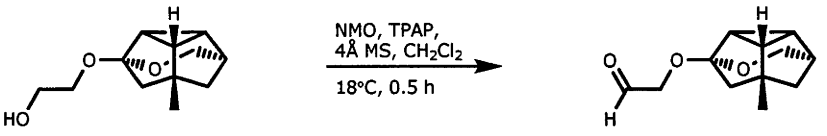
2-[(1*R*,2*R*,3*S*,4*S*,5*R*,7*R*)-7-Methyl-9-oxatetracyclo[3.3.2.0^{2,4}.0^{3,7}]oct-1-yloxy]ethanol (192).



189 **192**

A solution of ester **189** (30 mg, 126 μmol) in dichloromethane (3.2 ml) was cooled to -78°C then DIBAL (0.21 ml of a 1 M solution in dichloromethane, 210 μmol, 1.67 eq) was added dropwise. The resulting mixture was stirred at -78°C and after 0.3 h the reaction mixture was quenched with potassium sodium tartrate (3 ml of a saturated aq. solution) and allowed to warm to 18°C. Stirring was continued at this temperature for 1 h then the phases were separated. The aqueous layer was extracted with dichloromethane (3 x 5 ml) and the combined organic phases were dried (magnesium sulfate), filtered and concentrated under reduced pressure to give a clear, colourless oil (20 mg). ^{1}H NMR analysis of this material showed that it was composed of alcohol **192** containing traces of alcohol **191** and partially deprotected product **190**.

2-[(1*R*,2*R*,3*S*,4*S*,5*R*,7*R*)-7-Methyl-9-oxatetracyclo[3.3.2.0^{2,4}.0^{3,7}]oct-1-yloxy]acetaldehyde (193).



192 **193**

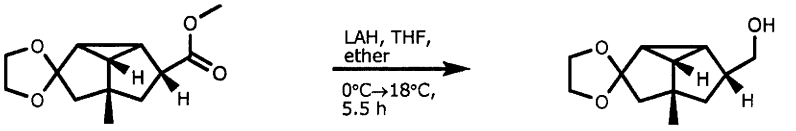
A solution of alcohol **192** (51 mg, 243 μmol) in dichloromethane (0.48 ml) was added to activated 4 Å molecular sieves (120 mg). The resulting heterogenous mixture was stirred while NMO (43 mg, 365 μmol, 1.5 eq) and TPAP (4 mg, 12 μmol, 5 mol%) were added. Stirring continued at 18°C for 0.5 h then the reaction mixture was filtered through a pad of silica and concentrated under reduced pressure. The grey oil thus obtained was subjected to column chromatography (silica, 1:7:12 v/v/v MeOH/ethyl acetate/hexane) to afford two fractions, A and B.

Concentration of fraction A yielded an unidentified compound (8 mg) as a clear, colourless oil.

Concentration of fraction B afforded a light-yellow oil that was resubjected to column chromatography (silica, 1:2 v/v ethyl acetate/hexane). Concentration of the appropriate fractions then gave aldehyde **193** (29 mg, 57%) as a clear, colourless oil.

R_f = 0.6 in 1:1 v/v ethyl acetate/hexane;
^{1}H NMR (300 MHz, $CDCl_3$): δ 9.72 (dd, J = 2.0 and 1.5 Hz, 1H), 4.18-4.05 (complex m, 2H), 3.77-3.66 (complex m, 2H), 2.56-2.49 (complex m, 1H), 2.20 (dd, J = 11.3 and 2.7 Hz, 1H), 2.02 (dddd, J = 12.2, 9.3, 2.7 and 0.7 Hz, 1H), 1.87-1.75 (complex m, 1H), 1.79 (t, J = 7.0 Hz, 1H), 1.75 (dd, J = 11.3 and 1.5 Hz, 1H), 1.57 (ddd, J = 8.4, 7.0 and 1.0 Hz, 1H), 1.48 (d, J = 12.2 Hz, 1H), 1.24 (s, 3H);
^{13}C NMR (75 MHz, $CDCl_3$): δ 202.2 (CH), 106.5 (C), 70.3 (CH_2), 67.4 (CH_2), 59.9 (CH_2), 51.5 (CH_2), 46.6 (C), 35.7 (CH), 34.8 (CH), 26.5 (CH), 26.0 (CH), 23.9 (CH_3);
IR ν_{max} (KBr) 2952, 2925, 2868, 1732, 1453, 1378, 1361, 1343, 1324, 1307, 1187, 1168, 1154, 1115, 1089, 1066, 1039, 1021, 1004, 978, 955, 942, 927, 877, 858 cm^{-1};
MS (EI, 70 eV) *m/z*: 208 ($M^{+\cdot}$, 21%), 149 (100), 107 (52), 105 (49), 93 (55), 91 (77), 79 (61), 43 (68);
HREIMS Found: $M^{+\cdot}$, 208.1099. Calculated for $C_{12}H_{16}O_3$ $M^{+\cdot}$, 208.1099.
Optical rotation $[\alpha]_D^{19}$ -23.1 (*c* 0.45, $CHCl_3$).

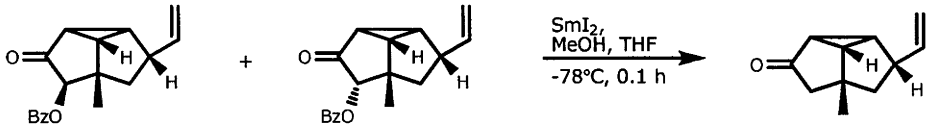
[(1*S*,2*S*,3*R*,5*R*,8*R*)-7,7-Ethylenedioxy-5-methyltricyclo[3.3.0.0^{2,8}]oct-3-yl]methanol (191)



189 **191**

LAH (0.07 ml of a 1 M solution in diethyl ether, 70 μmol, 1.1 eq) was cooled to 0°C then a solution of ester **189** (15 mg, 63 μmol) in THF (1 ml) was added dropwise. The reaction was stirred at 0°C for 1.5 h and at 18°C for 4 h then quenched with distilled water (0.06 ml) followed by addition of sodium hydroxide (0.06 ml of a 5% aq. solution). More distilled water was added (~ 0.12 ml) and stirring continued for 1 h after which the mixture was filtered. Concentration of the filtrate under reduced pressure afforded a colourless semi-solid that contained alcohol **191** (19 mg) as the sole product, as determined by ^{1}H NMR analysis.

(1*S*,2*R*,5*R*,7*S*,8*R*)-5-Methyl-7-vinyltricyclo[3.3.0.0^{2,8}]octan-3-one (194).

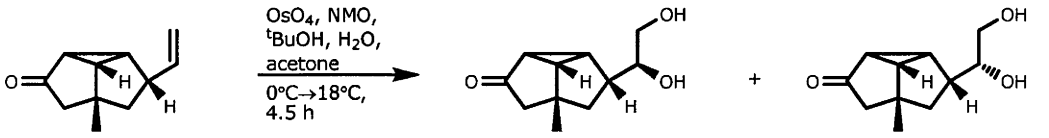


176a **176b** **194**

A solution of diquinanes **176a** and **176b** (296 mg, 1.05 mmol) in THF (10.5 ml) and methanol (5.3 ml) was cooled to -78°C then samarium diiodide (23.1 ml of a 0.1 M solution in THF, 2.31 mmol, 2.2 eq) was added dropwise. Stirring was continued at -78°C for 0.1 h then the reaction mixture was quenched with potassium carbonate (20 ml of a saturated aq. solution) before being allowed to slowly warm to 18°C. The separated aqueous phase was extracted with diethyl ether (3 x 50 ml) and the combined organic phases were washed with brine (1 x 20 ml) then dried (magnesium sulfate), filtered and concentrated under reduced pressure. The yellow oil (289 mg) thus obtained was subjected to column chromatography (silica, 1:39 v/v ethyl acetate/dichloromethane) and concentration of the appropriate fractions then gave diquinane **194** (93 mg, 54%) as a clear, colourless oil.

R_f = 0.5 in 1:39 v/v ethyl acetate/dichloromethane;
^{1}H NMR (300 MHz, $CDCl_3$): δ 5.82 (ddd, J = 17.2, 10.3 and 5.8 Hz, 1H), 5.08 (dt, J = 17.2 and 1.7 Hz, 1H), 4.97 (dt, J 10.3 and 1.7 Hz, 1H), 3.37-3.26 (complex m, 1H), 2.45 (ddd, J = 6.3, 4.9 and 0.8 Hz, 1H), 2.33-2.22 (complex m, 2H), 2.20-2.04 (complex m, 2H), 1.96 (dddd, J = 9.6, 4.9, 1.9 and 1.1 Hz, 1H), 1.63 (d, J = 12.6 Hz, 1H), 1.36 (s, 3H);
^{13}C NMR (125 MHz, $CDCl_3$): δ 215.5 (C), 139.9 (CH), 115.0 (CH_2), 55.0 (CH_2), 52.4 (CH_2), 46.3 (C), 43.4 (CH), 42.3 (CH), 39.6 (CH), 36.8 (CH), 25.7 (CH_3);
IR ν_{max} (KBr) 2954, 2928, 2870, 1724, 1454, 1407, 1331, 1313, 1250, 1197, 1096, 989, 965, 914, 885, 871 cm^{-1};
MS (EI, 70 eV) *m/z*: 162 ($M^{+\cdot}$, 11%), 120 (50), 105 (100), 77 (45);
HREIMS Found: $M^{+\cdot}$, 162.1044. Calculated for $C_{11}H_{14}O$ $M^{+\cdot}$, 162.1045.
Optical rotation $[\alpha]_D^{19}$ +74.0 (*c* 0.6, $CHCl_3$).

(1*S*,2*R*,5*R*,7*R*,8*S*)-5-Methyl-7-[(1*S*)-1,2-dihydroxyethyl]tricyclo-[3.3.0.0^{2,8}]-octan-3-one (195a) and (1*S*,2*R*,5*R*,7*R*,8*S*)-5-Methyl-7-[(1*R*)-1,2-dihydroxyethyl]tricyclo[3.3.0.0^{2,8}]-octan-3-one (195b).



194 **195a** **195b**

A solution of diquinane **194** (52 mg, 321 μmol) in acetone (1 ml) and water (1 ml) was cooled to 0°C then NMO (45 mg, 385 μmol, 1.2 eq) and osmium tetroxide (1.22 ml of a 0.1 M solution in *tert*-butanol, 122 μmol, 0.38 eq) were added. The resulting mixture was allowed to reach 18°C and after 4.5 h at this temperature it was quenched with sodium hydrogensulfite (4 ml of a saturated aq. solution) then stirred at 18°C for another hour. The resulting mixture was diluted with diethyl ether (4 ml) and just enough water to dissolve any solids. Solid sodium chloride was added to saturate the aqueous phase which, after separation, was extracted with diethyl ether (3 x 10 ml) then dichloromethane (3 x 10 ml). The combined organic extracts were then dried (magnesium sulfate), filtered and concentrated under reduced pressure. Subjection of the resulting clear, colourless oil to column chromatography (silica, ethyl acetate → 1:9 v/v MeOH/ethyl acetate) and concentration of the appropriate fractions then gave a 1:1 mixture of product epimers **195a** and **195b** (30 mg, 48%) as a clear, colourless oil.

R_f = 0.4 in 1:9 v/v MeOH/ethyl acetate;

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.84 (dd, J = 11.3 and 2.2 Hz, 0.5H), 3.66-3.58 (complex m, 0.5H), 3.50 (broad s, 2H), 3.45 (dd, J = 11.3 and 7.4 Hz, 0.5H), 3.40-3.30 (complex m, 1.5H), 2.71-2.55 (complex m, 1H), 2.54-2.48 (complex m, 1H), 2.43-2.30 (complex m, 1H), 2.27-1.80 (complex m, 5H), 1.37 (s, 1.5H), 1.36 (s, 1.5H);

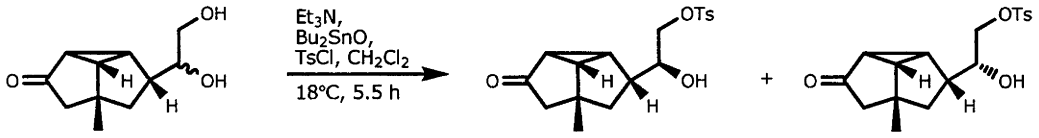
^{13}C NMR (75 MHz, $CDCl_3$): δ 217.6 (C), 217.4 (C), 74.2 (CH), 74.1 (CH), 66.2 (CH_2), 65.4 (CH_2), 56.4 (CH_2), 56.0 (CH_2), 48.8 (CH_2), 48.6 (CH_2), 46.6 (C), 46.2 (C), 43.8 (2xCH), 42.9 (CH), 42.8 (CH), 39.3 (CH), 39.1 (CH), 37.1 (CH), 35.4 (CH), 25.9 (CH_3), 25.8 (CH_3);

IR ν_{max} (KBr) 3405, 2951, 2928, 2871, 1709, 1454, 1408, 1379, 1360, 1335, 1312, 1254, 1200, 1161, 1101, 1076, 1041, 964, 920, 879, 813, 735 cm^{-1};

MS (EI, 70 eV) *m/z*: 196 ($M^{+\cdot}$, 2%), 178 [$(M-H_2O\cdot)^+$, 14], 165 (75), 136 (96), 95 (94), 94 (88), 93 (100), 91 (77), 43 (75);

HREIMS Found: $M^{+\cdot}$, 196.1098. Calculated for $C_{11}H_{16}O_3$ $M^{+\cdot}$, 196.1099.

(*S*)-2-Hydroxy-2-[(1*S*,2*S*,3*R*,5*R*,8*R*)-5-methyl-7-oxotricyclo[3.3.0.0^{2,8}]-oct-3-yl]ethyl 4-methylbenzenesulfonate (196a) and (*R*)-2-Hydroxy-2-[(1*S*,2*S*,3*R*,5*R*,8*R*)-5-methyl-7-oxotricyclo[3.3.0.0^{2,8}]oct-3-yl]ethyl 4-methylbenzenesulfonate (196b).



195 **196a** **196b**

Dibutyltin(IV)oxide (8 mg, 32 μmol, 0.21 eq) then triethylamine (21 μl, 153 μmol, 1 eq) were added to a solution of a 1:1 mixture of diols **195a** and **195b** (30 mg, 153 μmol) in dichloromethane (0.45 ml). Stirring was continued at 18°C for 0.15 h then a solution of tosyl chloride (29 mg, 152 μmol, 1 eq) in dichloromethane (ca. 0.25 ml) was added dropwise over a period of 0.15 h. After 5 h at 18°C the reaction mixture was diluted with dichloromethane (0.4 ml) then filtered through a plug of Celite™ and the filtrate concentrated under reduced pressure. The light-yellow oil (67 mg) thus obtained was subjected to column chromatography (silica, 1:3:6 v/v/v MeOH/ethyl acetate/hexane) to afford three fractions, A, B and C.

Concentration of fraction A (R_f = 0.4 in 1:3:6 v/v/v MeOH/ethyl acetate/hexane) yielded monotosylate **196a** (9 mg, 17%) as a clear, colourless oil.

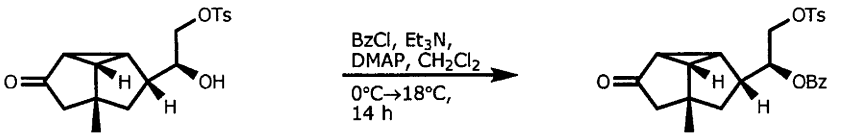
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.80 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 4.17 (dd, J = 10.4 and 4.6 Hz, 1H), 4.13 (dd, J = 10.4 and 2.7 Hz, 1H), 3.56-3.50 (complex m, 1H), 2.77-2.71 (complex m, 1H), 2.49 (dd, J = 5.9 and 5.3 Hz, 1H), 2.45 (s, 3H), 2.37 (ddd, J = 17.8, 2.3 and 1.2 Hz, 1H), 2.26-2.12 (complex m, 3H), 1.94-1.88 (complex m, 1H), 1.85 (dd, J = 9.8 and 5.3 Hz, 1H), 1.81 (d, J = 13.4 Hz, 1H), 1.38 (s, 3H);
^{13}C NMR (125 MHz, $CDCl_3$): δ 215.3 (C), 145.1 (C), 132.4 (C), 130.0 (CH), 128.0 (CH), 72.7 (CH_2), 71.4 (CH), 56.0 (CH_2), 48.6 (CH_2), 46.3 (C), 43.8 (CH), 42.3 (CH), 38.9 (CH), 34.6 (CH), 25.9 (CH_3), 21.7 (CH_3);
IR ν_{max} (KBr) 3418, 2954, 2926, 2870, 1715, 1598, 1453, 1406, 1357, 1309, 1254, 1189, 1176, 1098, 1019, 972, 957, 917, 878, 855, 814, 735, 667, 555 cm^{-1};
MS (EI, 70 eV) *m/z*: 350 ($M^{+\cdot}$, 1%), 165 (31), 155 (33), 136 (100), 105 (45), 93 (51), 91 (80);
HREIMS Found: $M^{+\cdot}$, 350.1182. Calculated for $C_{18}H_{22}O_5S$ $M^{+\cdot}$, 350.1188.
Optical rotation $[\alpha]_D^{20}$ +26.4 (*c* 0.64, $CHCl_3$).

Concentration of fraction B afforded a *ca.* 1:1.5 mixture of monotosylates **196a** and **196b** (29 mg, 54%) as a clear, colourless oil.

Concentration of fraction C (R_f = 0.3 in 1:3:6 v/v/v MeOH/ethyl acetate/hexane) gave monotosylate **196b** (3 mg, 6%) as a clear, colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78 (d, J = 8.0 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 4.06 (dd, J = 10.5 and 2.7 Hz, 1H), 3.90 (dd, J = 10.5 and 6.3 Hz, 1H), 3.58-3.52 (complex m, 1H), 2.73-2.66 (complex m, 1H), 2.55-2.48 (complex m, 2H), 2.45 (s, 3H), 2.40 (dd, J 17.8 and 2.2 Hz, 1H), 2.18-2.02 (complex m, 3H), 1.99 (dd, J = 9.5 and 5.2 Hz, 1H), 1.37 (s, 3H), 1.33 (d, J = 13.4 Hz, 1H);
^{13}C NMR (125 MHz, $CDCl_3$): δ 215.3 (C), 145.1 (C), 132.7 (C), 129.9 (CH), 127.9 (CH), 73.1 (CH_2), 71.3 (CH), 56.4 (CH_2), 48.6 (CH_2), 46.6 (C), 43.6 (CH), 42.1 (CH), 39.0 (CH), 35.7 (CH), 25.8 (CH_3), 21.7 (CH_3);
IR ν_{max} (KBr) 3420, 2956, 2918, 2870, 2850, 1712, 1598, 1453, 1358, 1312, 1189, 1176, 1097, 972, 957, 946, 918, 880, 853, 815, 667, 555 cm^{-1};
MS (EI, 70 eV) *m/z*: 350 ($M^{+\bullet}$, 5%), 165 (47), 136 (100), 93 (68), 91 (95), 43 (67), 32 (48);
HREIMS Found: $M^{+\bullet}$, 350.1188. Calculated for $C_{18}H_{22}O_5S$ $M^{+\bullet}$, 350.1188.
Optical rotation $[\alpha]_D^{20}$ +25.7 (*c* 0.35, $CHCl_3$).

(*S*)-1-[(1*S*,2*S*,3*R*,5*R*,8*R*)-5-Methyl-7-oxotricyclo[3.3.0.0^{2,8}]oct-3-yl]-2-(tosyloxy)ethyl benzoate (197a).



196a **197a**

A solution of monotosylate **196a** (7 mg, 20 μmol) in dichloromethane (0.7 ml) was cooled to 0°C then triethylamine (14 μl, 100 μmol, 5 eq.) was added followed by DMAP (200 μg, 2 μmol, 0.1 eq) and benzoyl chloride (5 μl, 40 μmol, 2 eq). The resulting mixture was allowed to warm to 18°C then stirred at this temperature for 14 h before being quenched with sodium hydrogen carbonate (1 ml of a saturated aq. solution). The separated aqueous phase was extracted with dichloromethane (5 x 2 ml) then the combined organic phases were dried (magnesium sulfate), filtered and concentrated under reduced pressure. The clear, colourless oil (5 mg) thus obtained was subjected to column chromatography (silica, 1:3:6 v/v/v MeOH/ethyl acetate/hexane) and concentration of the appropriate fractions then gave compound **197a** (3 mg, 35%) as a white, crystalline solid.

***R*$_f$** = 0.5 in 1:3:6 v/v/v MeOH/ethyl acetate/hexane;

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.92 (dd, *J* = 8.3 and 1.2 Hz, 2H), 7.73 (d, *J* = 8.3 Hz, 2H), 7.59-7.55 (complex m, 1H), 7.42 (dd, *J* = 8.3 Hz, 2H), 7.20 (d, *J* = 8.3 Hz, 2H), 4.98 (m, *J* = 11.1 Hz, 1H), 4.44 (dd, *J* = 11.2 and 2.6 Hz, 1H), 4.24 (dd, *J* = 11.2 and 2.2 Hz, 1H), 3.24 (m, 1H), 2.54 (dd, *J* = 5.9 and 5.3 Hz, 1H), 2.40 (dd, *J* = 18.1 and 1.0 Hz, 1H), 2.34 (s, 3H), 2.30 (d, *J* = 18.1 Hz, 1H), 2.20 (ddd, *J* = 13.2, 10.7 and 2.0 Hz, 1H), 2.11-2.06 (complex m, 1H), 1.95 (dd, *J* = 9.8 and 5.3 Hz, 1H), 1.55 (d, *J* = 13.2 Hz, 1H), 1.36 (s, 3H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 214.8 (C), 165.5 (C), 144.9 (C), 133.3 (CH), 132.3 (C), 129.9 (CH), 129.8 (CH), 129.5 (C), 128.3 (CH), 127.9 (CH), 73.0 (CH), 69.7 (CH_2), 55.3 (CH_2), 48.7 (CH_2), 46.5 (C), 42.3 (CH), 41.1 (CH), 39.0 (CH), 34.0 (CH), 25.8 (CH_3), 21.6 (CH_3);

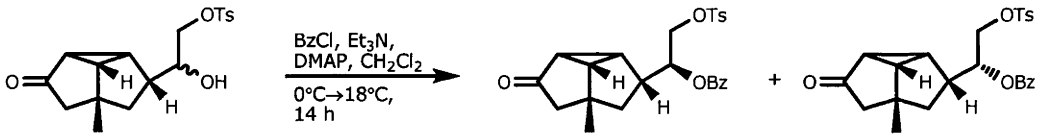
IR ν_{max} (KBr) 2956, 2927, 1720, 1599, 1452, 1364, 1270, 1190, 1177, 1109, 1097, 1070, 1026, 962, 946, 922, 881, 814, 793, 714, 667, 554 cm^{-1};

MS (EI, 70 eV) *m/z*: 454 ($M^{+\cdot}$, 4%), 149 (18), 118 (55), 105 (100), 91 (27), 77 (34), 57 (32), 43 (35);

HREIMS Found: $M^{+\cdot}$, 454.1447. Calculated for $C_{25}H_{26}O_6S$ $M^{+\cdot}$, 454.1450.

Optical rotation $[\alpha]_D^{20}$ +14.2 (*c* 0.38, $CHCl_3$).

(*S*)-1-[(1*S*,2*S*,3*R*,5*R*,8*R*)-5-Methyl-7-oxotricyclo[3.3.0.0^{2,8}]oct-3-yl]-2-(tosyloxy)ethyl benzoate (197a) and (*R*)-1-[(1*S*,2*S*,3*R*,5*R*,8*R*)-5-methyl-7-oxotricyclo[3.3.0.0^{2,8}]oct-3-yl]-2-(tosyloxy)ethyl benzoate (197b).



196 **197a** **197b**

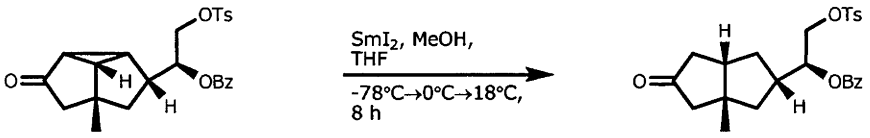
A magnetically stirred solution of a *ca.* 1:1.5 mixture of monotosylates **196a** and **196b** (29 mg, 83 μmol) in dichloromethane (2.9 ml) was treated in the same way as described above for the reaction of **196a**. The clear, colourless oil (51 mg) thus obtained was subjected to column chromatography (silica, 1:3:6 v/v/v MeOH/ethyl acetate/hexane) to afford two fractions, A and B.

Concentration of fraction A (R_f = 0.5 in 1:3:6 v/v/v MeOH/ethyl acetate/ hexane) gave adduct **197a** (15 mg, 40%) as a white, crystalline solid. This material was identical, in all respects, with an authentic sample.

Concentration of fraction B (R_f = 0.4 in 1:3:6 v/v/v MeOH/ethyl acetate/ hexane) afforded adduct **197b** (21 mg, 55%) as a white, crystalline solid, m.p. 134-139°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.97-7.93 (complex m, 2H), 7.70-7.66 (complex m, 2H), 7.60-7.54 (complex m, 1H), 7.45-7.40 (complex m, 2H), 7.15-7.12 (complex m, 2H), 4.87 (dt, *J* = 11.2 and 2.9 Hz, 1H), 4.31 (dd, *J* = 11.4 and 2.9 Hz, 1H), 4.17 (dd, *J* = 11.4 and 2.9 Hz, 1H), 3.34 (m, 1H), 2.51 (t, *J* = 5.4 Hz, 1H), 2.44-2.30 (complex m, partly concealed, 1H), 2.34-2.24 (complex m, partly concealed, 1H), 2.30 (s, 3H), 2.15-2.07 (complex m, partly concealed, 1H), 2.07 (d, *J* = 17.0 Hz, 1H), 1.87 (dd, *J* = 10.2 and 5.4 Hz, 1H), 1.44 (d, *J* = 13.2 Hz, 1H), 1.39 (s, 3H);
^{13}C NMR (75 MHz, $CDCl_3$): δ 213.7 (C), 165.1 (C), 145.0 (C), 133.2 (CH), 132.1 (C), 129.9 (CH), 129.8 (CH), 129.5 (C), 128.2 (CH), 127.8 (CH), 73.2 (CH), 69.4 (CH_2), 56.2 (CH_2), 47.8 (CH_2), 46.5 (C), 42.1 (CH), 40.9 (CH), 38.9 (CH), 35.6 (CH), 25.8 (CH_3), 21.6 (CH_3);
IR ν_{max} (KBr) 2956, 1723, 1599, 1451, 1361, 1312, 1266, 1189, 1176, 1109, 1096, 1069, 1025, 957, 946, 921, 884, 839, 814, 713, 667, 554 cm^{-1};
MS (EI, 70 eV) *m/z*: 454 ($M^{+\bullet}$, 3%), 283 (16), 118 (72), 105 (100), 91 (36), 77 (41);
HREIMS Found: $M^{+\bullet}$, 454.1448. Calculated for $C_{25}H_{26}O_6S$ $M^{+\bullet}$, 454.1450.

(*S*)-1-[(2*S*,3a*R*,6a*S*)-3a-Methyl-5-oxooctahydropentalen-2-yl]-2-(tosyloxy)ethyl benzoate (198a).



197a **198a**

A solution of diquinane **197a** (15 mg, 33 μmol) in THF/MeOH (0.6 ml of a 2:1 v/v mixture) was cooled to -78°C then samarium diiodide (0.4 ml of a 0.1 M solution in THF, 40 μmol, 1.2 eq) was added dropwise over 0.25 h. The resulting mixture was stirred at -78°C for 0.67 h then warmed to 0°C and stirred at this temperature for 3 h then at 18°C for 1 h. The reaction mixture was then re-cooled to -78°C and additional samarium diiodide (0.4 ml of a 0.1 M solution in THF, 40 μmol, 1.2 eq) was added dropwise over 0.03 h. The reaction mixture was stirred at -78°C for 0.02 h and then allowed to warm to room temperature. After 0.5 h at 18°C, samarium diiodide (0.4 ml of a 0.1 M solution in THF, 40 μmol, 1.2 eq) was again added and after another 0.5 h the reaction was quenched with potassium carbonate (1 ml of a saturated aq. solution). The separated aqueous phase was extracted with diethyl ether (3 x 5 ml) then the combined organic phases were dried (magnesium sulfate), filtered and concentrated under reduced pressure. The yellow oil (17 mg) so obtained contained only a by-product. Accordingly, the aqueous phase was saturated with sodium chloride and extracted with dichloromethane (3 x 5 ml). The combined organic phases were dried (magnesium sulfate), filtered and concentrated under reduced pressure. The resulting yellow oil was subjected to column chromatography (silica, 1:3:6 v/v/v MeOH/ethyl acetate/hexane) and concentration of the appropriate fractions then gave adduct **198a** (3 mg, 21%) as a clear, colourless oil.

R_f = 0.5 in 1:3:6 v/v/v MeOH/ethyl acetate/hexane;
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93-7.89 (complex m, 2H), 7.73-7.69 (complex m, 2H), 7.61-7.56 (complex m, 1H), 7.46-7.42 (complex m, 2H), 7.20-7.16 (complex m, 2H), 5.12 (ddd, J = 7.8, 4.5 and 3.4 Hz, 1H), 4.21 (dd, J = 11.1 and 3.4 Hz, 1H), 4.17 (dd, J = 11.1 and 4.5 Hz, 1H), 2.72-2.62 (complex m, 1H), 2.53 (ddd, J = 19.0, 9.3 and 1.5 Hz, 1H), 2.34 (s, 3H), 2.34-2.14 (complex m, 4H), 2.05 (ddd, J = 19.0, 4.6 and 1.5 Hz, 1H), 1.84 (dd, J = 13.2 and 7.8 Hz, 1H), 1.58 (dd, J = 13.2 and 10.7 Hz, 1H), 1.22-1.14 (complex m, 1H), 1.18 (s, 3H);
^{13}C NMR (125 MHz, $CDCl_3$): δ 219.0 (C), 165.6 (C), 145.0 (C), 133.4 (CH), 132.4 (C), 129.8 (CH), 129.7 (CH), 129.4 (C), 128.4 (CH), 127.9 (CH), 74.2 (CH), 69.5

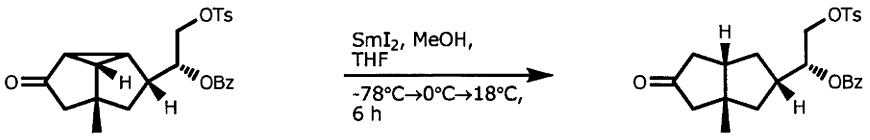
(CH_2), 52.4 (CH_2), 46.7 (CH), 46.2 (C), 44.4 (CH_2), 42.4 (CH_2), 39.7 (CH), 36.3 (CH_2), 27.7 (CH_3), 21.6 (CH_3);

IR ν_{max} (KBr) 2953, 1738, 1722, 1451, 1364, 1269, 1190, 1177, 1109, 1097, 1070, 976, 942, 815, 714, 667, 554 cm^{-1};

MS (ESI, +ve ion mode) *m/z*: 495 [$(M+K)^+$, 7%], 479 [$(M+Na)^+$, 100], 455 (38), 285 (93), 206 (35), 163 (50), 135 (35), 105 (69);

HRESMS Found: $(M+Na)^+$, 479.1500. Calculated for $C_{25}H_{28}O_6S$ $(M+Na)^+$, 479.1504.

(*R*)-1-[(2*S*,3a*R*,6a*S*)-3a-Methyl-5-oxooctahydropentalen-2-yl]-2-(tosyloxy)ethyl benzoate (198b).



197b **198b**

A solution of diquinane **197b** (21 mg, 46 μmol) in THF/MeOH (0.9 ml of a 2:1 v/v mixture) was cooled to -78°C and samarium diiodide (0.55 ml of a 0.1 M solution in THF, 55 μmol, 1.2 eq) was added dropwise over 0.08 h. The resulting mixture was stirred at -78°C until the blue colour of the solution turned to yellow (ca. 0.4-1 h). More samarium diiodide (0.55 ml of a 0.1 M solution in THF, 55 μmol, 1.2 eq) was added dropwise and the reaction warmed to 0°C then further samarium diiodide was added to re-establish a deep blue colour. The reaction was warmed to 18°C and stirred at this temperature until the blue colour faded. As the colour faded, more samarium diiodide (0.55 ml of a 0.1 M solution in THF, 55 μmol, 1.2 eq) was added and this was repeated at 18°C until the starting material had become consumed, as determined by TLC analysis. The reaction was then quenched with potassium carbonate (1 ml of a saturated aq. solution). The separated aqueous phase was extracted with diethyl ether (3 x 5 ml) and then with dichloromethane (3 x 5 ml). The combined organic phases were dried (magnesium sulfate), filtered and concentrated under reduced pressure. The yellow oil thus obtained was subjected to column chromatography (silica, 1:3:6 v/v/v MeOH/ethyl acetate/hexane) and concentration of the appropriate fractions then gave adduct **198b** (11 mg, 52%) as a clear, colourless oil.

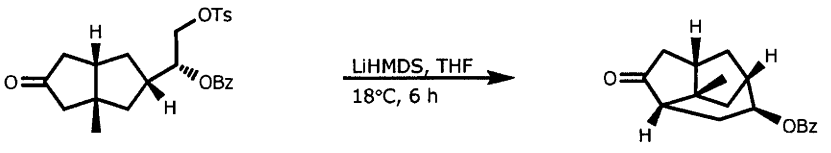
R_f = 0.6 in 1:3:6 v/v/v MeOH/ethyl acetate/hexane;
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.94-7.88 (complex m, 2H), 7.74-7.68 (complex m, 2H), 7.62-7.55 (complex m, 1H), 7.47-7.40 (complex m, 2H), 7.21-7.15 (complex m, 2H), 5.11 (m, 1H), 4.22 (dd, J = 11.1 and 3.4 Hz, 1H), 4.15 (dd, J = 11.1 and 4.6 Hz, 1H), 2.74-2.57 (complex m, 1H), 2.52 (ddd, J = 18.8, 8.8 and 1.2 Hz, 1H), 2.34 (s, 3H), 2.36-2.08 (complex m, 4H), 2.07 (dd, J = 18.8 and 4.8 Hz, 1H), 1.79 (dd, J = 12.9 and 8.0 Hz, 1H), 1.41 (dd, J = 12.9 and 11.1 Hz, 1H), 1.41-1.30 (complex m, 1H), 1.18 (s, 3H);
^{13}C NMR (75 MHz, $CDCl_3$): δ 219.0 (C), 165.6 (C), 145.0 (C), 133.3 (CH), 132.3 (C), 129.8 (CH), 129.7 (CH), 129.4 (C), 128.4 (CH), 127.8 (CH), 74.3 (CH), 69.5 (CH_2), 52.4 (CH_2), 46.7 (CH), 46.3 (C), 44.2 (CH_2), 42.5 (CH_2), 39.7 (CH), 36.3 (CH_2), 27.7 (CH_3), 21.6 (CH_3);

IR ν_{max} (KBr) 3020, 2954, 2918, 2848, 1736, 1727, 1452, 1364, 1269, 1216, 1190, 1177, 1110, 1097, 814, 756, 713, 667, 554 cm^{-1};

MS (EI, 70 eV) *m/z*: 456 ($M^{+\bullet}$, <1%), 285 (11), 179 (21), 162 (25), 105 (100), 91 (34), 77 (32);

HREIMS Found: $M^{+\bullet}$, 456.1606. Calculated for $C_{25}H_{28}O_6S$ $M^{+\bullet}$, 456.1607.

[(1*S*,2*S*,4*S*,7*S*,8*S*)-8-Methyl-5-oxotricyclo[5.2.1.0^{4,8}]dec-2-yl] benzoate (200b).



198b **200b**

A magnetically stirred solution of adduct **198b** (10 mg, 22 μmol) in THF (0.2 ml) was cooled to -78°C and LiHMDS (26 μl of a 1 M solution in THF, 26 μmol, 1.2 eq) was added dropwise. After 0.5 h, the reaction mixture was warmed to 0°C and after 1 h to 18°C. After 5 h at this temperature the reaction mixture was quenched with water (0.2 ml). The separated aqueous phase was washed with dichloromethane (5 x 1 ml) then the combined organic layers were dried (magnesium sulfate), filtered and concentrated under reduced pressure. The resulting light-yellow oil was subjected to column chromatography (silica, 1:3:6 v/v/v MeOH/ethyl acetate/hexane) to afford two fractions, A and B.

Concentration of fraction A (R_f = 0.7 in 1:3:6 v/v/v MeOH/ethyl acetate/hexane) gave tricycle **200b** (3 mg, 50%) as a white, crystalline solid, m.p. 128-133°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.04-7.99 (complex m, 2H), 7.58-7.52 (complex m, 1H), 7.47-7.40 (complex m, 2H), 4.73 (t, *J* = 8.1 Hz, 1H), 2.56 (dd, *J* = 18.3 and 7.8 Hz, 1H), 2.48-2.17 (complex m, 4H), 2.10 (d, *J* = 9.1 Hz, 1H), 1.96 (d, *J* 12.3 Hz, 1H), 1.76 (dt, *J* = 13.7 and 9.1 Hz, 2H), 1.45 (dd, *J* = 12.3, 4.5 and 1.1 Hz, 1H), 1.26 (s, 3H), 1.19-1.11 (complex m, 1H);
^{13}C NMR (75 MHz, $CDCl_3$): δ 222.6 (C), 165.8 (C), 132.9 (CH), 130.5 (C), 129.5 (CH), 128.3 (CH), 75.8 (CH), 50.9 (CH), 47.0 (C), 44.3 (CH_2), 43.1 (CH), 41.3 (CH), 38.4 (CH_2), 36.0 (CH_2), 25.8 (CH_2), 25.0 (CH_3);
IR ν_{max} (KBr) 2930, 1732, 1717, 1451, 1336, 1313, 1275, 1258, 1179, 1143, 1112, 1068, 1024, 1003, 981, 710 cm^{-1};
MS (EI, 70 eV) *m/z*: 284 [M$^{+\bullet}$, 3%], 163 (45), 162 (89), 134 (52), 106 (44), 105 (100), 93 (89), 92 (63), 77 (83);
HREIMS Found: M$^{+\bullet}$, 284.1412. Calculated for M$^{+\bullet}$ $C_{18}H_{20}O_3$, 284.1412.

A sample of this material was recrystallised (ethyl acetate/hexane) to provide material suitable for single-crystal X-ray analysis.

Concentration of fraction B (R_f = 0.6 in 1:3:6 v/v/v MeOH/ethyl acetate/ hexane) gave starting material **198b** (1 mg, 9% recovery) as a clear, colourless oil that was identical, in all respects, with an authentic sample.

5.5 References

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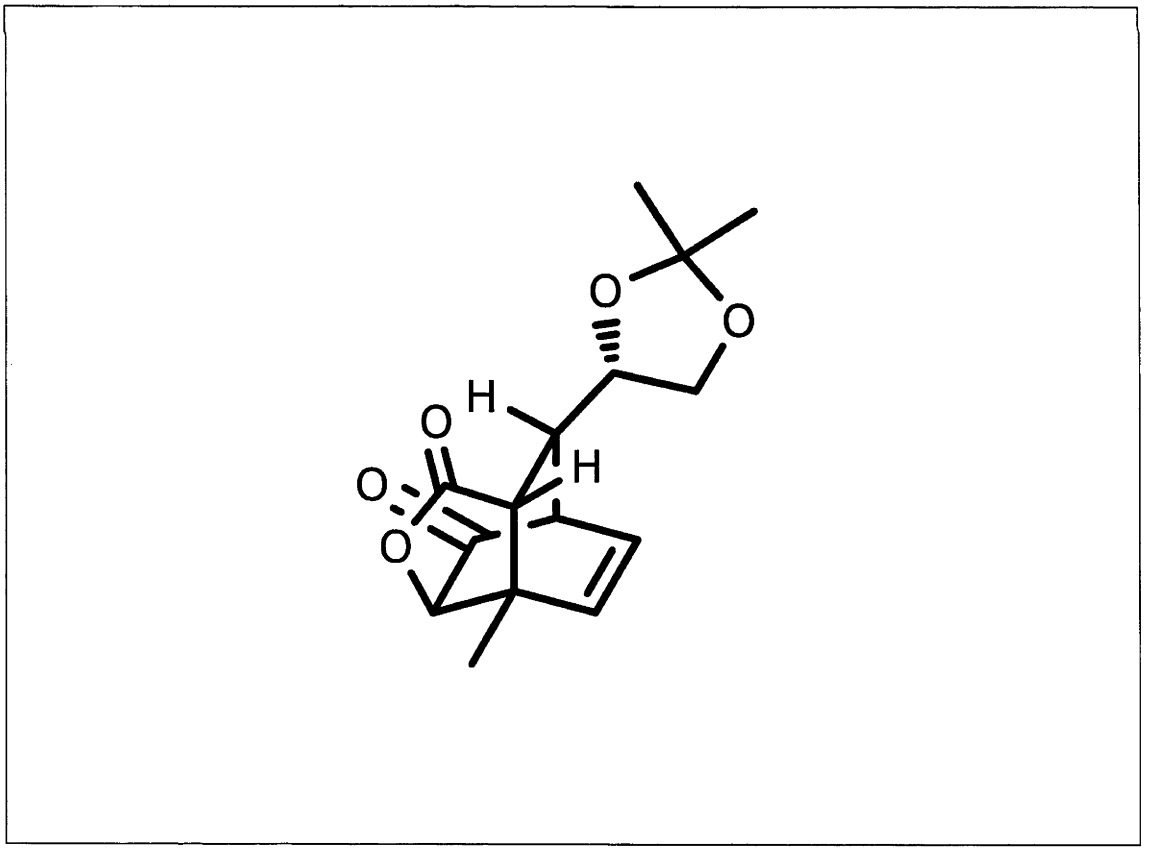
Appendix A

A.1 X-ray crystal structure report for compound 132



Sample: ban0811

Compound: $C_{15}H_{18}O_5$

X-ray Structure Report

for

Christine Dietinger and Martin G. Banwell

by

Anthony C. Willis

Research School of Chemistry,

The Australian National University, Canberra, ACT 0200, Australia

Friday, 30th May, 2008

Figure Captions for $C_{15}H_{18}O_5$

Figure 1. Molecular structure of $C_{15}H_{18}O_5$ with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

Figure 2. Unit cell packing diagram of $C_{15}H_{18}O_5$ projected down the *a* axis. Hydrogen atoms are drawn as circles with small radii.

Assignment of Chiral Centres

C3	R	C4	S	C5	R	C7	R
C10	S	C11	S				

Calculated by PLATON.
Spek, A.L. (2001). PLATON - A Multipurpose Crystallographic Tool, Utrecht University, Utrecht, The Netherlands.

Crystal structure of $C_{15}H_{18}O_5$ — ban0811

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Research School of Chemistry, The Australian National University, Canberra, A. C. T. 0200, Australia

Correspondence email: **willis@rsc.anu.edu.au**

Abstract

The crystal structure of $C_{15}H_{18}O_5$ is reported.

Comment

The compound is enantiometrically pure but the anomolous dispersion terms are very low for all elements in the structure and so the absolute configuration can not be determined in this experiment. Consequently Friedel-pair reflections have been averaged and the Flack parameter has not been refined. The absolute configuration of the molecule has been assigned on the basis of the synthetic precursors.

The crystallographic asymmetric unit consists of one molecule of $C_{15}H_{18}O_5$.

Experimental

The compound was prepared by CD and recrystallized from hexane/benzene. The sample ID is 6CD34p18recr.

Refinement

All hydrogen atoms were observed in difference electron density maps prior to their inclusion. They were added at calculated locations and then refined positionally.

The final difference electron density map is essentially featureless with the largest peaks lying on C—C bonds.

Computing details

Data collection: *COLLECT* (Nonius, 1997-2001).; cell refinement: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *CRYSTALS* (Betteridge *et al.*, 2003); molecular graphics: *ORTEP*II (Johnson 1976) in *TEXSAN* (MSC, 1992-1997); software used to prepare material for publication: *CRYSTALS* (Betteridge *et al.*, 2003).

(ban0811)

Crystal data

$C_{15}H_{18}O_5$	$V = 1389.23\ (6)$ Å^3
$M_r = 278.30$	$Z = 4$
Orthorhombic, $P2_12_12_1$	Mo $K\alpha$
$a = 9.4716\ (2)$ Å	$\mu = 0.10$ mm^{-1}
$b = 10.4131\ (3)$ Å	$T = 200$ K
$c = 14.0855\ (3)$ Å	0.31 × 0.22 × 0.20 mm

Data collection

Nonius KappaCCD diffractometer	2315 independent reflections
Absorption correction: integration via Gaussian method (Coppens, 1970) implemented in maXus (2000)	1819 reflections with $I > 2.0\sigma(I)$
$T_{min} = 0.980$, $T_{max} = 0.985$	$R_{int} = 0.031$
19113 measured reflections	

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.031$	$\Delta\rho_{max} = 0.26$ e Å^{-3}
$wR(F^2) = 0.070$	$\Delta\rho_{min} = -0.20$ e Å^{-3}
$S = 0.86$	Absolute structure: from synthesis
2308 reflections	
235 parameters	
Only H-atom coordinates refined	

Table 1
Selected geometric parameters (Å, °)

O1—C2	1.369 (2)	C7—C8	1.505 (2)
O1—C5	1.460 (2)	C7—C10	1.558 (2)
C2—C3	1.514 (2)	C8—C9	1.320 (2)
C2—O16	1.1951 (19)	C10—C11	1.5182 (19)
C3—C4	1.554 (2)	C11—O12	1.4315 (17)
C3—C10	1.5597 (19)	C11—C15	1.522 (2)
C4—C5	1.539 (2)	O12—C13	1.4335 (17)
C4—C9	1.507 (2)	C13—O14	1.4202 (18)
C4—C17	1.526 (2)	C13—C19	1.507 (2)
C5—C6	1.541 (2)	C13—C20	1.499 (2)
C6—C7	1.520 (2)	O14—C15	1.4153 (19)
C6—O18	1.2029 (19)		
C2—O1—C5	107.99 (12)	C6—C7—C10	108.05 (12)
O1—C2—C3	108.60 (13)	C8—C7—C10	108.81 (12)
O1—C2—O16	121.20 (15)	C7—C8—C9	114.85 (15)
C3—C2—O16	130.17 (16)	C4—C9—C8	116.56 (15)
C2—C3—C4	101.46 (12)	C7—C10—C3	108.69 (11)

C2—C3—C10	107.62 (12)	C7—C10—C11	112.05 (11)
C4—C3—C10	110.68 (11)	C3—C10—C11	111.11 (11)
C3—C4—C5	96.31 (11)	C10—C11—O12	107.13 (11)
C3—C4—C9	112.49 (12)	C10—C11—C15	115.32 (13)
C5—C4—C9	108.58 (13)	O12—C11—C15	102.12 (11)
C3—C4—C17	112.49 (14)	C11—O12—C13	107.79 (11)
C5—C4—C17	112.43 (14)	O12—C13—O14	106.40 (11)
C9—C4—C17	113.31 (14)	O12—C13—C19	111.05 (13)
C4—C5—O1	104.95 (12)	O14—C13—C19	108.05 (14)
C4—C5—C6	109.35 (13)	O12—C13—C20	108.05 (13)
O1—C5—C6	106.02 (13)	O14—C13—C20	110.50 (15)
C5—C6—C7	111.65 (13)	C19—C13—C20	112.62 (16)
C5—C6—O18	122.50 (14)	C13—O14—C15	109.50 (11)
C7—C6—O18	125.85 (14)	C11—C15—O14	104.04 (12)
C6—C7—C8	103.33 (12)		

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supplementary materials

Crystal structure of $C_{15}H_{18}O_5$ — ban0811

Christine Dietinger, Martin G. Banwell and Anthony C. Willis

(ban0811)

Crystal data

$C_{15}H_{18}O_5$	$D_x = 1.331$ Mg m^{-3}
$M_r = 278.30$	Mo $K\alpha$ radiation $\lambda = 0.71073$ Å
Orthorhombic, $P2_12_12_1$	Cell parameters from 9442 reflections
$a = 9.4716$ (2) Å	$\theta = 2.6$–$30°$
$b = 10.4131$ (3) Å	$\mu = 0.10$ mm^{-1}
$c = 14.0855$ (3) Å	$T = 200$ K
$V = 1389.23$ (6) Å^3	Block, colourless
$Z = 4$	0.31 × 0.22 × 0.20 mm
$F_{000} = 592$	

Data collection

Nonius KappaCCD diffractometer	1819 reflections with $I > 2.0\sigma(I)$
Monochromator: graphite	$R_{int} = 0.031$
$T = 200$ K	$\theta_{max} = 30.1°$
φ and ω scans with CCD	$\theta_{min} = 2.6°$
Absorption correction: integration via Gaussian method (Coppens, 1970) implemented in maXus (2000)	$h = -13 \rightarrow 13$
$T_{min} = 0.980$, $T_{max} = 0.985$	$k = -14 \rightarrow 14$
19113 measured reflections	$l = -19 \rightarrow 19$
2315 independent reflections	

Refinement

Refinement on F^2	Hydrogen site location: inferred from neighbouring sites
Least-squares matrix: full	Only H-atom coordinates refined
$R[F^2 > 2\sigma(F^2)] = 0.031$	Method = Modified Sheldrick $w = 1/[\sigma^2(F^2) + (0.03P)^2 + 0.0P]$, where $P = (\max(F_o^2,0) + 2F_c^2)/3$
$wR(F^2) = 0.070$	$(\Delta/\sigma)_{max} = 0.010$
$S = 0.86$	$\Delta\rho_{max} = 0.26$ e Å^{-3}
2308 reflections	$\Delta\rho_{min} = -0.20$ e Å^{-3}
235 parameters	Extinction correction: None
Primary atom site location: structure-invariant direct methods	Absolute structure: from synthesis

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters ($Å^2$)

	x	y	z	U_{iso}*/U_{eq}
O1	0.06389 (12)	0.77324 (10)	0.49140 (8)	0.0363
C2	0.11073 (16)	0.65478 (16)	0.51946 (12)	0.0322
C3	0.12779 (15)	0.57112 (14)	0.43233 (10)	0.0250
C4	0.01406 (15)	0.62859 (15)	0.36506 (11)	0.0283
C5	0.04403 (17)	0.77027 (15)	0.38862 (11)	0.0315
C6	0.18684 (15)	0.80968 (15)	0.34505 (11)	0.0301
C7	0.26886 (15)	0.69385 (14)	0.30938 (11)	0.0272
C8	0.17490 (17)	0.63986 (16)	0.23300 (12)	0.0339
C9	0.04755 (17)	0.60605 (16)	0.26179 (11)	0.0345
C10	0.27892 (14)	0.59475 (13)	0.39197 (10)	0.0227
C11	0.34684 (14)	0.46976 (14)	0.36046 (10)	0.0253
O12	0.36284 (11)	0.39150 (10)	0.44332 (8)	0.0331
C13	0.48144 (15)	0.30845 (15)	0.42823 (11)	0.0288
O14	0.56214 (13)	0.36460 (12)	0.35408 (10)	0.0526
C15	0.49829 (16)	0.48115 (16)	0.32530 (12)	0.0307
O16	0.13506 (15)	0.63210 (14)	0.60101 (8)	0.0474
C17	−0.13532 (17)	0.5881 (2)	0.39239 (16)	0.0423
O18	0.22539 (13)	0.91963 (10)	0.34131 (9)	0.0446
C19	0.4343 (2)	0.17736 (19)	0.39584 (16)	0.0463
C20	0.5654 (2)	0.3038 (2)	0.51833 (14)	0.0479
H31	0.1148 (19)	0.4823 (17)	0.4484 (11)	0.0299*
H51	−0.032 (2)	0.8291 (18)	0.3728 (11)	0.0378*
H71	0.3584 (19)	0.7217 (16)	0.2870 (11)	0.0325*
H81	0.2128 (19)	0.6347 (17)	0.1681 (13)	0.0407*
H91	−0.024 (2)	0.5690 (18)	0.2212 (13)	0.0412*
H101	0.3387 (18)	0.6316 (15)	0.4397 (11)	0.0272*
H111	0.2894 (18)	0.4248 (16)	0.3152 (12)	0.0303*
H151	0.5459 (18)	0.5515 (18)	0.3586 (12)	0.0368*
H152	0.509 (2)	0.4852 (17)	0.2553 (13)	0.0368*
H171	−0.201 (2)	0.6382 (19)	0.3573 (13)	0.0505*
H172	−0.154 (2)	0.6019 (19)	0.4639 (15)	0.0505*
H173	−0.150 (2)	0.497 (2)	0.3794 (13)	0.0505*
H191	0.521 (2)	0.127 (2)	0.3826 (14)	0.0556*
H192	0.377 (2)	0.135 (2)	0.4446 (15)	0.0556*
H193	0.380 (2)	0.191 (2)	0.3378 (15)	0.0556*
H201	0.653 (2)	0.251 (2)	0.5099 (15)	0.0573*
H202	0.598 (2)	0.389 (2)	0.5312 (15)	0.0573*
H203	0.498 (2)	0.265 (2)	0.5717 (15)	0.0573*

Atomic displacement parameters ($Å^2$)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0387 (6)	0.0317 (6)	0.0386 (6)	0.0039 (5)	0.0082 (5)	−0.0056 (5)
C2	0.0270 (7)	0.0347 (8)	0.0350 (8)	−0.0032 (7)	0.0060 (6)	0.0001 (7)

C3	0.0227 (6)	0.0221 (7)	0.0300 (7)	−0.0001 (6)	0.0027 (6)	0.0033 (6)
C4	0.0193 (6)	0.0287 (7)	0.0370 (8)	0.0002 (6)	−0.0010 (6)	0.0016 (7)
C5	0.0265 (7)	0.0280 (7)	0.0401 (8)	0.0075 (6)	0.0031 (7)	0.0026 (7)
C6	0.0300 (7)	0.0259 (7)	0.0343 (8)	0.0020 (6)	−0.0016 (6)	0.0043 (6)
C7	0.0232 (6)	0.0255 (7)	0.0330 (7)	0.0000 (6)	0.0051 (6)	0.0056 (6)
C8	0.0375 (8)	0.0359 (8)	0.0284 (7)	0.0054 (7)	−0.0016 (7)	0.0030 (7)
C9	0.0331 (8)	0.0366 (9)	0.0338 (8)	0.0012 (7)	−0.0095 (7)	0.0010 (7)
C10	0.0194 (6)	0.0212 (6)	0.0277 (7)	−0.0008 (5)	−0.0002 (6)	0.0006 (6)
C11	0.0224 (6)	0.0234 (7)	0.0301 (7)	0.0013 (6)	−0.0008 (6)	−0.0002 (6)
O12	0.0292 (5)	0.0290 (6)	0.0412 (6)	0.0099 (5)	0.0126 (5)	0.0107 (5)
C13	0.0258 (7)	0.0281 (7)	0.0324 (7)	0.0071 (6)	0.0042 (6)	0.0021 (6)
O14	0.0403 (6)	0.0521 (8)	0.0655 (8)	0.0246 (6)	0.0289 (7)	0.0281 (7)
C15	0.0291 (7)	0.0285 (7)	0.0346 (8)	0.0053 (7)	0.0086 (6)	0.0040 (7)
O16	0.0571 (8)	0.0558 (8)	0.0294 (6)	−0.0034 (7)	0.0043 (6)	0.0013 (5)
C17	0.0220 (7)	0.0446 (10)	0.0603 (12)	−0.0034 (8)	0.0009 (8)	0.0030 (9)
O18	0.0445 (6)	0.0243 (5)	0.0649 (8)	−0.0009 (5)	0.0059 (6)	0.0040 (5)
C19	0.0399 (9)	0.0376 (10)	0.0615 (12)	0.0075 (9)	−0.0014 (10)	−0.0133 (9)
C20	0.0487 (10)	0.0482 (11)	0.0467 (10)	0.0155 (10)	−0.0124 (9)	−0.0111 (9)

Geometric parameters (Å, °)

O1—C2	1.369 (2)	C10—H101	0.959 (17)
O1—C5	1.460 (2)	C11—O12	1.4315 (17)
C2—C3	1.514 (2)	C11—C15	1.522 (2)
C2—O16	1.1951 (19)	C11—H111	0.960 (17)
C3—C4	1.554 (2)	O12—C13	1.4335 (17)
C3—C10	1.5597 (19)	C13—O14	1.4202 (18)
C3—H31	0.960 (17)	C13—C19	1.507 (2)
C4—C5	1.539 (2)	C13—C20	1.499 (2)
C4—C9	1.507 (2)	O14—C15	1.4153 (19)
C4—C17	1.526 (2)	C15—H151	0.979 (18)
C5—C6	1.541 (2)	C15—H152	0.993 (17)
C5—H51	0.973 (19)	C17—H171	0.95 (2)
C6—C7	1.520 (2)	C17—H172	1.03 (2)
C6—O18	1.2029 (19)	C17—H173	0.98 (2)
C7—C8	1.505 (2)	C19—H191	1.00 (2)
C7—C10	1.558 (2)	C19—H192	0.98 (2)
C7—H71	0.950 (18)	C19—H193	0.98 (2)
C8—C9	1.320 (2)	C20—H201	1.00 (2)
C8—H81	0.983 (18)	C20—H202	0.96 (2)
C9—H91	0.969 (19)	C20—H203	1.06 (2)
C10—C11	1.5182 (19)		
O1···C10^{i}	3.446 (2)	O14···O18^{iv}	3.457 (2)
O1···C17^{ii}	3.589 (2)	O18···C19^{v}	3.422 (2)
O12···C20^{iii}	3.516 (2)	O18···C9^{vi}	3.544 (2)
O14···C7^{iv}	3.320 (2)	O18···C15^{vii}	3.573 (2)
C2—O1—C5	107.99 (12)	C3—C10—H101	110.4 (9)
O1—C2—C3	108.60 (13)	C11—C10—H101	107.3 (10)

O1—C2—O16	121.20 (15)	C10—C11—O12	107.13 (11)
C3—C2—O16	130.17 (16)	C10—C11—C15	115.32 (13)
C2—C3—C4	101.46 (12)	O12—C11—C15	102.12 (11)
C2—C3—C10	107.62 (12)	C10—C11—H111	111.9 (10)
C4—C3—C10	110.68 (11)	O12—C11—H111	108.9 (10)
C2—C3—H31	110.4 (10)	C15—C11—H111	110.8 (10)
C4—C3—H31	115.2 (10)	C11—O12—C13	107.79 (11)
C10—C3—H31	110.8 (10)	O12—C13—O14	106.40 (11)
C3—C4—C5	96.31 (11)	O12—C13—C19	111.05 (13)
C3—C4—C9	112.49 (12)	O14—C13—C19	108.05 (14)
C5—C4—C9	108.58 (13)	O12—C13—C20	108.05 (13)
C3—C4—C17	112.49 (14)	O14—C13—C20	110.50 (15)
C5—C4—C17	112.43 (14)	C19—C13—C20	112.62 (16)
C9—C4—C17	113.31 (14)	C13—O14—C15	109.50 (11)
C4—C5—O1	104.95 (12)	C11—C15—O14	104.04 (12)
C4—C5—C6	109.35 (13)	C11—C15—H151	109.6 (10)
O1—C5—C6	106.02 (13)	O14—C15—H151	107.9 (10)
C4—C5—H51	114.7 (11)	C11—C15—H152	115.2 (11)
O1—C5—H51	108.0 (10)	O14—C15—H152	106.0 (11)
C6—C5—H51	113.1 (10)	H151—C15—H152	113.3 (15)
C5—C6—C7	111.65 (13)	C4—C17—H171	109.1 (12)
C5—C6—O18	122.50 (14)	C4—C17—H172	111.3 (12)
C7—C6—O18	125.85 (14)	H171—C17—H172	108.7 (17)
C6—C7—C8	103.33 (12)	C4—C17—H173	110.8 (12)
C6—C7—C10	108.05 (12)	H171—C17—H173	109.9 (17)
C8—C7—C10	108.81 (12)	H172—C17—H173	107.1 (16)
C6—C7—H71	108.9 (10)	C13—C19—H191	106.9 (12)
C8—C7—H71	113.9 (10)	C13—C19—H192	111.2 (12)
C10—C7—H71	113.3 (10)	H191—C19—H192	110.3 (17)
C7—C8—C9	114.85 (15)	C13—C19—H193	106.2 (13)
C7—C8—H81	118.0 (11)	H191—C19—H193	110.9 (16)
C9—C8—H81	127.2 (11)	H192—C19—H193	111.2 (17)
C4—C9—C8	116.56 (15)	C13—C20—H201	110.8 (12)
C4—C9—H91	118.9 (11)	C13—C20—H202	107.7 (13)
C8—C9—H91	124.5 (11)	H201—C20—H202	105.4 (19)
C7—C10—C3	108.69 (11)	C13—C20—H203	107.0 (11)
C7—C10—C11	112.05 (11)	H201—C20—H203	111.7 (17)
C3—C10—C11	111.11 (11)	H202—C20—H203	114.2 (17)
C7—C10—H101	107.2 (9)		
O1—C2—C3—C4	−29.2 (1)	C3—C10—C7—C6	51.3 (1)
O1—C2—C3—C10	87.0 (1)	C3—C10—C7—C8	−60.3 (1)
O1—C5—C4—C3	−42.0 (1)	C3—C10—C11—C15	−176.5 (1)
O1—C5—C4—C9	−158.3 (1)	C4—C3—C10—C7	12.4 (2)
O1—C5—C4—C17	75.5 (2)	C4—C3—C10—C11	−111.4 (1)
O1—C5—C6—O18	−78.3 (2)	C4—C5—C6—C7	−11.2 (2)
O1—C5—C6—C7	101.4 (1)	C4—C9—C8—C7	1.2 (2)
O12—C11—C10—C3	−63.6 (1)	C5—C4—C3—C10	−72.4 (1)
O12—C11—C10—C7	174.6 (1)	C5—C4—C9—C8	53.8 (2)
O12—C11—C15—O14	30.4 (1)	C5—C6—C7—C8	62.4 (2)

O12—C13—O14—C15	1.6 (2)	C5—C6—C7—C10	−52.8 (2)
O14—C13—O12—C11	19.1 (1)	C6—C5—C4—C9	−44.9 (2)
O14—C15—C11—C10	146.2 (1)	C6—C5—C4—C17	−171.1 (1)
O16—C2—O1—C5	−179.9 (2)	C6—C7—C8—C9	−59.1 (2)
O16—C2—C3—C4	153.0 (2)	C6—C7—C10—C11	174.4 (1)
O16—C2—C3—C10	−90.7 (2)	C7—C10—C11—C15	61.7 (2)
O18—C6—C5—C4	169.0 (1)	C8—C7—C10—C11	62.9 (1)
O18—C6—C7—C8	−117.9 (2)	C8—C9—C4—C17	179.5 (2)
O18—C6—C7—C10	126.9 (2)	C9—C4—C3—C10	40.7 (2)
C2—O1—C5—C4	26.6 (2)	C9—C8—C7—C10	55.6 (2)
C2—O1—C5—C6	−89.1 (1)	C10—C3—C4—C17	170.1 (1)
C2—C3—C4—C5	41.6 (1)	C10—C11—O12—C13	−151.9 (1)
C2—C3—C4—C9	154.7 (1)	C11—O12—C13—C19	−98.3 (1)
C2—C3—C4—C17	−75.9 (2)	C11—O12—C13—C20	137.8 (1)
C2—C3—C10—C7	−97.7 (1)	C11—C15—O14—C13	−20.0 (2)
C2—C3—C10—C11	138.6 (1)	C13—O12—C11—C15	−30.3 (1)
C3—C2—O1—C5	2.0 (2)	C15—O14—C13—C19	120.9 (1)
C3—C4—C5—C6	71.4 (1)	C15—O14—C13—C20	−115.5 (2)
C3—C4—C9—C8	−51.5 (2)		

Symmetry codes: (i) $x-1/2, -y+3/2, -z+1$; (ii) $x+1/2, -y+3/2, -z+1$; (iii) $x-1/2, -y+1/2, -z+1$; (iv) $-x+1, y-1/2, -z+1/2$; (v) $x, y+1, z$; (vi) $-x, y+1/2, -z+1/2$; (vii) $-x+1, y+1/2, -z+1/2$.

Sample: ban0621

Compound: $C_{15}H_{20}O_3$

X-ray Structure Report

for

Christine Dietinger and Martin G. Banwell

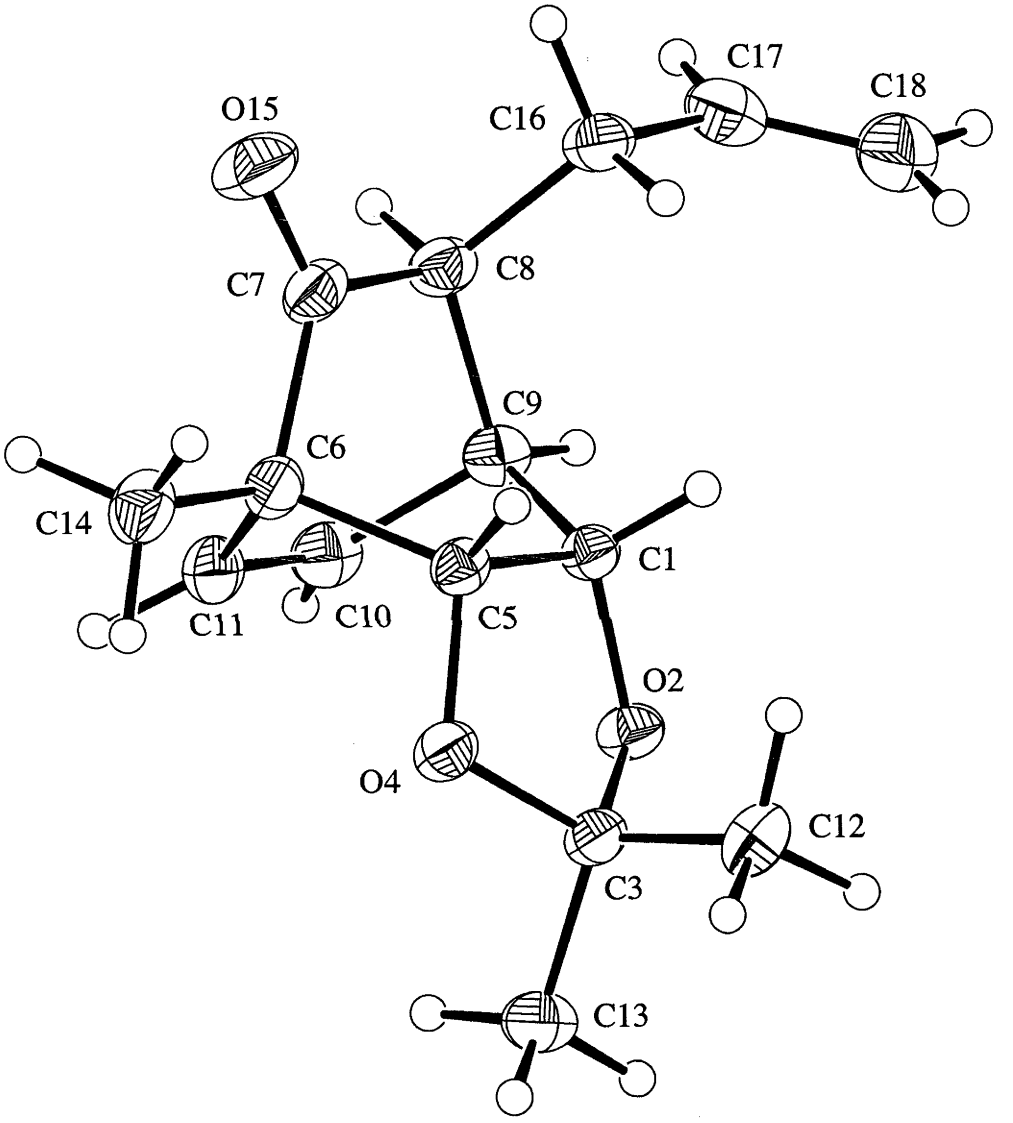
by

Anthony C. Willis

Research School of Chemistry, Institute of Advanced Studies

Australian National University, Canberra, ACT 0200, Australia

Friday, 14th July, 2006


C17
C18
O15
C16
C8
C7
C9
C6
C14
C1
C11
C10
C5
O2
O4
C12
C3
C13

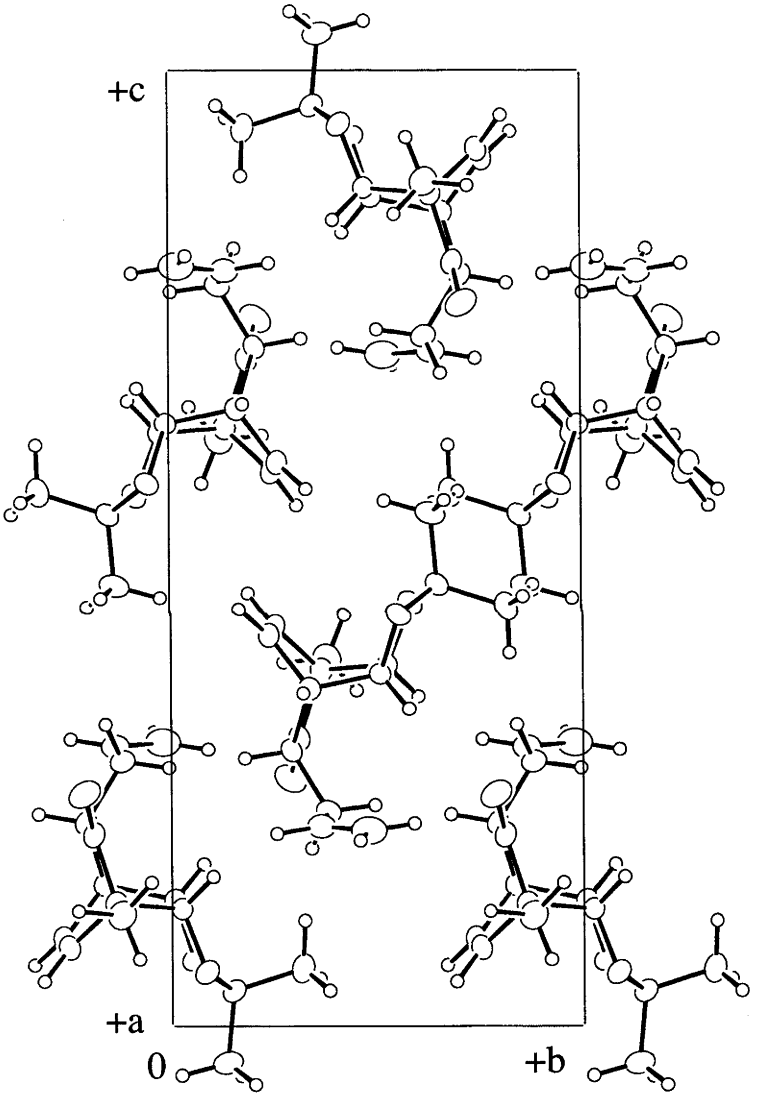

+c
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Figure Captions for $C_{15}H_{20}O_3$

Figure 1. Molecular structure of $C_{15}H_{20}O_3$ with labelling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

Figure 2. Unit cell packing diagram of $C_{15}H_{20}O_3$ projected down the *a* axis. Hydrogen atoms are drawn as circles with small radii.

Assignment of Chiral Centres

C1	S	C5	R	C6	S	C8	S
C9	S						

Calculated by PLATON.
Spek, A.L. (2001). PLATON - A Multipurpose Crystallographic Tool, Utrecht University, Utrecht, The Netherlands.

14 Jul 2006

Crystal structure of $C_{15}H_{20}O_3$ –ban0621

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Abstract

The crystal structure of $C_{15}H_{20}O_3$ is reported.

Comment

The compound is enantiometrically pure but the anomolous dispersion terms are very low for all elements in the structure and so the absolute configuration can not be determined in this experiment. Consequently Friedel-pair reflections have been averaged and the Flack parameter has not been refined. The absolute configuration of the molecule has been assigned on the basis of the synthetic precursors.

The crystallographic asymmetric unit consists of one molecule of $C_{15}H_{20}O_3$.

The final difference electron density map is essentially featureless, with the largest peaks being located between atoms.

Experimental

The compound was prepared by CD and recrystallized from hexane. The sample ID is 2CD81*p*56–62epimI_spota

Crystal data

$C_{15}H_{20}O_3$

$M_r = 248.32$

Orthorhombic

$P2_12_12_1$

$a = 8.0593\,(2)$ Å

$b = 8.5636\,(1)$ Å

$c = 19.9156\,(4)$ Å

$V = 1374.51\,(5)$ Å^3

$Z = 4$

$D_x = 1.200$ Mg m^{-3}

D_m not measured

Mo $K\alpha$ radiation

$\lambda = 0.71073$ Å

Cell parameters from 19710 reflections

$\theta = 3$–$27.5°$

$\mu = 0.082$ mm^{-1}

$T = 200$ K

Plate

Colourless

$0.48 \times 0.22 \times 0.10$ mm

Crystal source: local

Data collection

Nonius KappaCCD diffractometer

φ and ω scans with CCD

Absorption correction:

by integration *via* Gaussian method (Coppens, 1970) implemented in maXus (2000)

$T_{min} = 0.972$, $T_{max} = 0.992$

28429 measured reflections

1824 independent reflections

1435 reflections with

$I > 2.0\sigma(I)$

$R_{int} = 0.036$

$\theta_{max} = 27.486°$

$h = -10 \rightarrow 10$

$k = -11 \rightarrow 9$

$l = -25 \rightarrow 25$

Refinement

Refinement on F

$R = 0.0270$

$wR = 0.0316$

$S = 1.1272$

1435 reflections

163 parameters

H-atom parameters not refined

Method, part 1, Chebychev polynomial, (Watkin, 1994, Prince, 1982)

[weight] = $1.0/[A_0{*}T_0(x) + A_1{*}T_1(x) \ldots + A_{n-1}]{*}T_{n-1}(x)]$

where A_i are the Chebychev coefficients listed below and x= Fcalc/Fmax Method = Robust Weighting (Prince, 1982) W = [weight] * [1-(deltaF/6*sigmaF)^2]^2 A_i are: 0.560 0.233 0.318

$(\Delta/\sigma)_{max} = 0.000253$

$\Delta\rho_{max} = 0.13$ e Å^{-3}

$\Delta\rho_{min} = -0.10$ e Å^{-3}

Extinction correction: none

Scattering factors from International Tables Vol C 4.2.6.8 and 6.1.1.4

Absolute structure: The enantiomer has been assigned by reference to an unchanging chiral centre in the synthetic procedure.

Table 1. *Selected geometric parameters (Å, °)*

O2—C1	1.4269 (17)	C6—C7	1.532 (2)
O2—C3	1.4244 (19)	C6—C11	1.516 (2)
O4—C3	1.4335 (18)	C6—C14	1.518 (2)
O4—C5	1.4172 (18)	C7—C8	1.524 (3)
O15—C7	1.209 (2)	C8—C9	1.548 (2)
C1—C5	1.545 (2)	C8—C16	1.541 (2)
C1—C9	1.535 (2)	C9—C10	1.509 (2)
C3—C12	1.516 (2)	C10—C11	1.324 (3)
C3—C13	1.503 (2)	C16—C17	1.487 (3)
C5—C6	1.552 (2)	C17—C18	1.310 (3)
C1—O2—C3	106.90 (11)	C5—C6—C14	112.07 (14)
C3—O4—C5	107.34 (11)	C7—C6—C14	112.79 (14)
O2—C1—C5	104.34 (12)	C11—C6—C14	114.86 (15)
O2—C1—C9	110.73 (12)	C6—C7—O15	123.35 (17)
C5—C1—C9	109.59 (13)	C6—C7—C8	113.97 (13)
O4—C3—O2	104.62 (11)	O15—C7—C8	122.67 (16)
O4—C3—C12	110.35 (14)	C7—C8—C9	108.02 (13)
O2—C3—C12	111.17 (13)	C7—C8—C16	110.53 (14)
O4—C3—C13	108.55 (13)	C9—C8—C16	115.68 (14)
O2—C3—C13	109.15 (14)	C1—C9—C8	107.26 (12)
C12—C3—C13	112.66 (14)	C1—C9—C10	107.64 (13)
C1—C5—O4	104.80 (12)	C8—C9—C10	107.29 (13)
C1—C5—C6	111.37 (12)	C9—C10—C11	115.03 (16)
O4—C5—C6	109.61 (12)	C6—C11—C10	115.97 (15)
C5—C6—C7	103.33 (12)	C8—C16—C17	112.61 (15)
C5—C6—C11	107.56 (12)	C16—C17—C18	124.7 (2)
C7—C6—C11	105.36 (13)		

H atoms were added at calculated positions and, during refinement, each rides on the C atom to which it is attached.

Data collection: *COLLECT* (Nonius BV, 1997). Cell refinement: Denzo/Scalepack . Data reduction: Denzo/Scalepack (Otwinowski & Minor, 1997). Program(s) used to solve structure: *SIR*92 (Altomare *et al.* 1994). Program(s) used to refine structure: *CRYSTALS* (Watkin *et al.*2003). Molecular graphics: *ORTEP*-II (Johnson 1976) in teXsan (MSC, 1992–1997) . Software used to prepare material for publication: *CRYSTALS* .

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Supplementary data

Table *S*1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å²)*

$$U_{\rm eq} = (1/3)\Sigma_i\Sigma_j U^{ij} a^i a^j \mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	$U_{\rm eq}$
O2	0.78310 (13)	0.55386 (13)	0.43105 (5)	0.0382
O4	0.50619 (13)	0.58455 (12)	0.44387 (5)	0.0398
O15	0.37306 (18)	0.28869 (17)	0.25815 (7)	0.0628
C1	0.71409 (19)	0.50780 (17)	0.36811 (7)	0.0335
C3	0.66277 (19)	0.64978 (18)	0.46334 (7)	0.0375
C5	0.52474 (19)	0.52501 (16)	0.37790 (7)	0.0337
C6	0.43546 (19)	0.36495 (18)	0.37228 (8)	0.0393
C7	0.4770 (2)	0.31130 (18)	0.30083 (8)	0.0434
C8	0.6621 (2)	0.29173 (18)	0.28769 (8)	0.0418
C9	0.7563 (2)	0.33674 (17)	0.35261 (7)	0.0385
C10	0.6868 (2)	0.23808 (19)	0.40874 (8)	0.0443
C11	0.5248 (2)	0.25160 (19)	0.41825 (8)	0.0451
C12	0.6758 (2)	0.81782 (19)	0.43992 (10)	0.0508
C13	0.6810 (2)	0.6336 (3)	0.53814 (8)	0.0536
C14	0.2502 (2)	0.3788 (2)	0.38452 (10)	0.0534
C16	0.7136 (2)	0.3811 (2)	0.22386 (8)	0.0473
C17	0.8931 (3)	0.3637 (3)	0.20826 (8)	0.0569
C18	0.9987 (3)	0.4796 (3)	0.20388 (11)	0.0733
H11	0.75401 (19)	0.57777 (17)	0.33130 (7)	0.0402
H51	0.47826 (19)	0.60022 (16)	0.34441 (7)	0.0404
H81	0.6829 (2)	0.17828 (18)	0.27929 (8)	0.0502
H91	0.8787 (2)	0.32118 (17)	0.34754 (7)	0.0462
H101	0.7578 (2)	0.16772 (19)	0.43667 (8)	0.0532
H111	0.4651 (2)	0.19072 (19)	0.45362 (8)	0.0542
H121	0.5901 (2)	0.88237 (19)	0.46333 (10)	0.0610
H122	0.7888 (2)	0.85915 (19)	0.45066 (10)	0.0610
H123	0.6572 (2)	0.82273 (19)	0.39032 (10)	0.0610
H131	0.5967 (2)	0.7008 (3)	0.56106 (8)	0.0643
H132	0.7949 (2)	0.6672 (3)	0.55182 (8)	0.0643
H133	0.6634 (2)	0.5222 (3)	0.55127 (8)	0.0643
H141	0.1976 (2)	0.2734 (2)	0.38045 (10)	0.0640
H142	0.2303 (2)	0.4211 (2)	0.43063 (10)	0.0640
H143	0.2005 (2)	0.4509 (2)	0.35055 (10)	0.0640
H161	0.6886 (2)	0.4945 (2)	0.23041 (8)	0.0568
H162	0.6477 (2)	0.3403 (2)	0.18510 (8)	0.0568
H171	0.9363 (3)	0.2557 (3)	0.20055 (8)	0.0683
H181	1.1178 (3)	0.4583 (3)	0.19315 (11)	0.0880
H182	0.9602 (3)	0.5892 (3)	0.21125 (11)	0.0880

Table *S*2. *Anisotropic displacement parameters* (Å²)

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O2	0.0354 (5)	0.0437 (6)	0.0356 (5)	0.0012 (5)	−0.0052 (4)	−0.0068 (4)
O4	0.0357 (6)	0.0416 (6)	0.0422 (6)	−0.0026 (5)	0.0009 (5)	−0.0099 (5)
O15	0.0581 (8)	0.0733 (9)	0.0569 (8)	−0.0075 (7)	−0.0161 (7)	−0.0198 (7)
C1	0.0347 (7)	0.0342 (7)	0.0316 (7)	−0.0019 (6)	−0.0031 (6)	−0.0014 (5)
C3	0.0352 (7)	0.0397 (7)	0.0376 (7)	−0.0031 (7)	−0.0014 (6)	−0.0082 (7)
C5	0.0361 (8)	0.0304 (6)	0.0346 (7)	0.0002 (6)	−0.0039 (6)	0.0001 (6)
C6	0.0398 (8)	0.0364 (7)	0.0417 (8)	−0.0064 (7)	−0.0030 (6)	−0.0009 (7)
C7	0.0511 (9)	0.0329 (7)	0.0462 (8)	−0.0067 (7)	−0.0074 (8)	−0.0051 (7)
C8	0.0529 (9)	0.0333 (8)	0.0393 (8)	0.0003 (7)	−0.0030 (7)	−0.0066 (6)
C9	0.0416 (8)	0.0352 (8)	0.0387 (7)	0.0056 (7)	−0.0025 (6)	−0.0018 (6)
C10	0.0579 (11)	0.0313 (7)	0.0437 (8)	0.0054 (7)	−0.0059 (7)	0.0012 (7)
C11	0.0579 (10)	0.0329 (7)	0.0447 (8)	−0.0070 (8)	−0.0009 (8)	0.0045 (7)
C12	0.0519 (10)	0.0381 (8)	0.0624 (11)	−0.0061 (7)	−0.0071 (9)	−0.0068 (8)
C13	0.0553 (10)	0.0676 (11)	0.0379 (8)	−0.0072 (10)	0.0009 (7)	−0.0089 (8)
C14	0.0407 (9)	0.0583 (10)	0.0611 (10)	−0.0120 (8)	−0.0018 (8)	−0.0054 (9)

C16	0.0601 (10)	0.0461 (9)	0.0358 (7)	−0.0039 (8)	−0.0053 (7)	−0.0055 (7)
C17	0.0709 (13)	0.0591 (11)	0.0407 (9)	0.0071 (11)	0.0075 (9)	−0.0007 (8)
C18	0.0689 (14)	0.0945 (17)	0.0566 (11)	−0.0177 (13)	−0.0005 (11)	−0.0003 (11)

Table *S*3. *Geometric parameters (Å, °)*

O2—C1	1.4269 (17)	C9—H91	1.000
O2—C3	1.4244 (19)	C10—C11	1.324 (3)
O4—C3	1.4335 (18)	C10—H101	1.000
O4—C5	1.4172 (18)	C11—H111	1.000
O15—C7	1.209 (2)	C12—H121	1.000
C1—C5	1.545 (2)	C12—H122	1.000
C1—C9	1.535 (2)	C12—H123	1.000
C1—H11	1.000	C13—H131	1.000
C3—C12	1.516 (2)	C13—H132	1.000
C3—C13	1.503 (2)	C13—H133	1.000
C5—C6	1.552 (2)	C14—H141	1.000
C5—H51	1.000	C14—H142	1.000
C6—C7	1.532 (2)	C14—H143	1.000
C6—C11	1.516 (2)	C16—C17	1.487 (3)
C6—C14	1.518 (2)	C16—H161	1.000
C7—C8	1.524 (3)	C16—H162	1.000
C8—C9	1.548 (2)	C17—C18	1.310 (3)
C8—C16	1.541 (2)	C17—H171	1.000
C8—H81	1.000	C18—H181	1.000
C9—C10	1.509 (2)	C18—H182	1.000
C1—O2—C3	106.90 (11)	C8—C9—H91	111.5
C3—O4—C5	107.34 (11)	C10—C9—H91	111.5
O2—C1—C5	104.34 (12)	C9—C10—C11	115.03 (16)
O2—C1—C9	110.73 (12)	C9—C10—H101	122.5
C5—C1—C9	109.59 (13)	C11—C10—H101	122.5
O2—C1—H11	110.7	C6—C11—C10	115.97 (15)
C5—C1—H11	110.7	C6—C11—H111	122.0
C9—C1—H11	110.7	C10—C11—H111	122.0
O4—C3—O2	104.62 (11)	C3—C12—H121	109.5
O4—C3—C12	110.35 (14)	C3—C12—H122	109.5
O2—C3—C12	111.17 (13)	H121—C12—H122	109.5
O4—C3—C13	108.55 (13)	C3—C12—H123	109.5
O2—C3—C13	109.15 (14)	H121—C12—H123	109.5
C12—C3—C13	112.66 (14)	H122—C12—H123	109.5
C1—C5—O4	104.80 (12)	C3—C13—H131	109.5
C1—C5—C6	111.37 (12)	C3—C13—H132	109.5
O4—C5—C6	109.61 (12)	H131—C13—H132	109.5
C1—C5—H51	110.3	C3—C13—H133	109.5
O4—C5—H51	110.3	H131—C13—H133	109.5
C6—C5—H51	110.3	H132—C13—H133	109.5
C5—C6—C7	103.33 (12)	C6—C14—H141	109.5
C5—C6—C11	107.56 (12)	C6—C14—H142	109.5
C7—C6—C11	105.36 (13)	H141—C14—H142	109.5
C5—C6—C14	112.07 (14)	C6—C14—H143	109.5
C7—C6—C14	112.79 (14)	H141—C14—H143	109.5
C11—C6—C14	114.86 (15)	H142—C14—H143	109.5
C6—C7—O15	123.35 (17)	C8—C16—C17	112.61 (15)
C6—C7—C8	113.97 (13)	C8—C16—H161	108.7
O15—C7—C8	122.67 (16)	C17—C16—H161	108.7
C7—C8—C9	108.02 (13)	C8—C16—H162	108.7
C7—C8—C16	110.53 (14)	C17—C16—H162	108.7
C9—C8—C16	115.68 (14)	H161—C16—H162	109.5
C7—C8—H81	107.4	C16—C17—C18	124.7 (2)
C9—C8—H81	107.4	C16—C17—H171	117.6
C16—C8—H81	107.4	C18—C17—H171	117.6
C1—C9—C8	107.26 (12)	C17—C18—H181	120.0
C1—C9—C10	107.64 (13)	C17—C18—H182	120.0
C8—C9—C10	107.29 (13)	H181—C18—H182	120.0
C1—C9—H91	111.5		

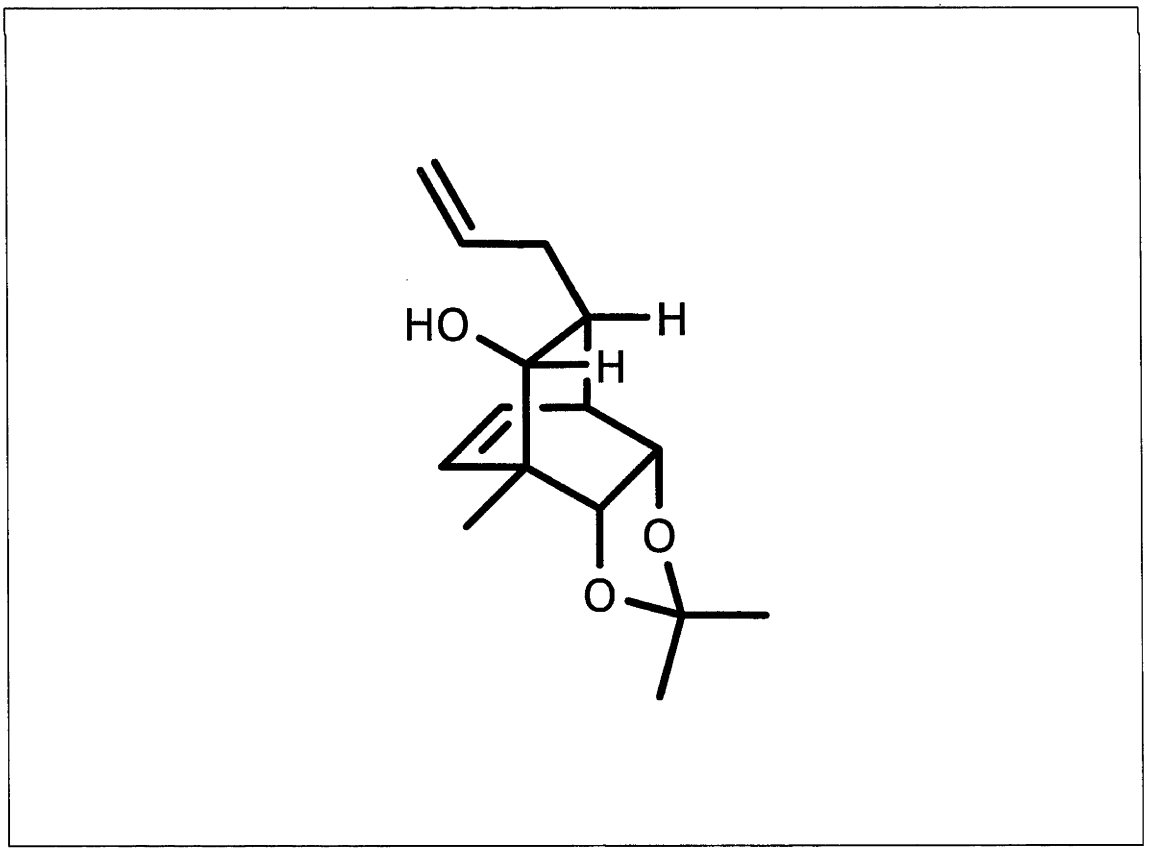
O2—C1—C5—O4	2.3 (1)	C3—O2—C1—C5	−22.5 (1)
O2—C1—C5—C6	−116.2 (1)	C3—O2—C1—C9	−140.4 (1)
O2—C1—C9—C8	174.2 (1)	C3—O4—C5—C6	138.3 (1)
O2—C1—C9—C10	59.0 (2)	C5—O4—C3—C12	86.5 (1)
O2—C3—O4—C5	−33.2 (1)	C5—O4—C3—C13	−149.6 (1)
O4—C3—O2—C1	34.6 (1)	C5—C1—C9—C8	59.6 (1)
O4—C5—C1—C9	120.9 (1)	C5—C1—C9—C10	−55.5 (2)
O4—C5—C6—C7	−176.1 (1)	C5—C6—C7—C8	60.5 (2)
O4—C5—C6—C11	−64.9 (2)	C5—C6—C11—C10	−54.2 (2)
O4—C5—C6—C14	62.2 (2)	C6—C5—C1—C9	2.4 (2)
O15—C7—C6—C5	−118.4 (2)	C6—C7—C8—C9	−1.1 (2)
O15—C7—C6—C11	128.9 (2)	C6—C7—C8—C16	−128.6 (1)
O15—C7—C6—C14	2.8 (2)	C6—C11—C10—C9	−0.8 (2)
O15—C7—C8—C9	177.8 (2)	C7—C6—C11—C10	55.5 (2)
O15—C7—C8—C16	50.3 (2)	C7—C8—C9—C10	55.0 (2)
C1—O2—C3—C12	−84.5 (1)	C7—C8—C16—C17	−179.1 (1)
C1—O2—C3—C13	150.6 (1)	C8—C7—C6—C11	−52.3 (2)
C1—C5—O4—C3	18.7 (1)	C8—C7—C6—C14	−178.3 (1)
C1—C5—C6—C7	−60.6 (1)	C8—C9—C10—C11	−57.3 (2)
C1—C5—C6—C11	50.6 (2)	C8—C16—C17—C18	−120.7 (2)
C1—C5—C6—C14	177.7 (1)	C9—C8—C16—C17	57.7 (2)
C1—C9—C8—C7	−60.4 (2)	C10—C9—C8—C16	179.4 (1)
C1—C9—C8—C16	64.0 (2)	C10—C11—C6—C14	−179.7 (1)
C1—C9—C10—C11	57.9 (2)		

Table *S4. Contact distances (Å)*

O4···C13^{i}	3.581 (2)	O15···C18^{iii}	3.598 (3)
O15···C1^{ii}	3.550 (2)	C13···C17^{iv}	3.440 (2)
O15···C16^{ii}	3.578 (2)		

Symmetry codes: (i) $x-\frac{1}{2},\frac{3}{2}-y,1-z$; (ii) $1-x,y-\frac{1}{2},\frac{1}{2}-z$; (iii) $x-1,y,z$; (iv) $\frac{3}{2}-x,1-y,\frac{1}{2}+z$.

A.3 X-ray crystal structure report for compound 146c



Sample: ban0623

Compound: $C_{15}H_{22}O_3$

X-ray Structure Report

for

Christine Dietinger and Martin G. Banwell

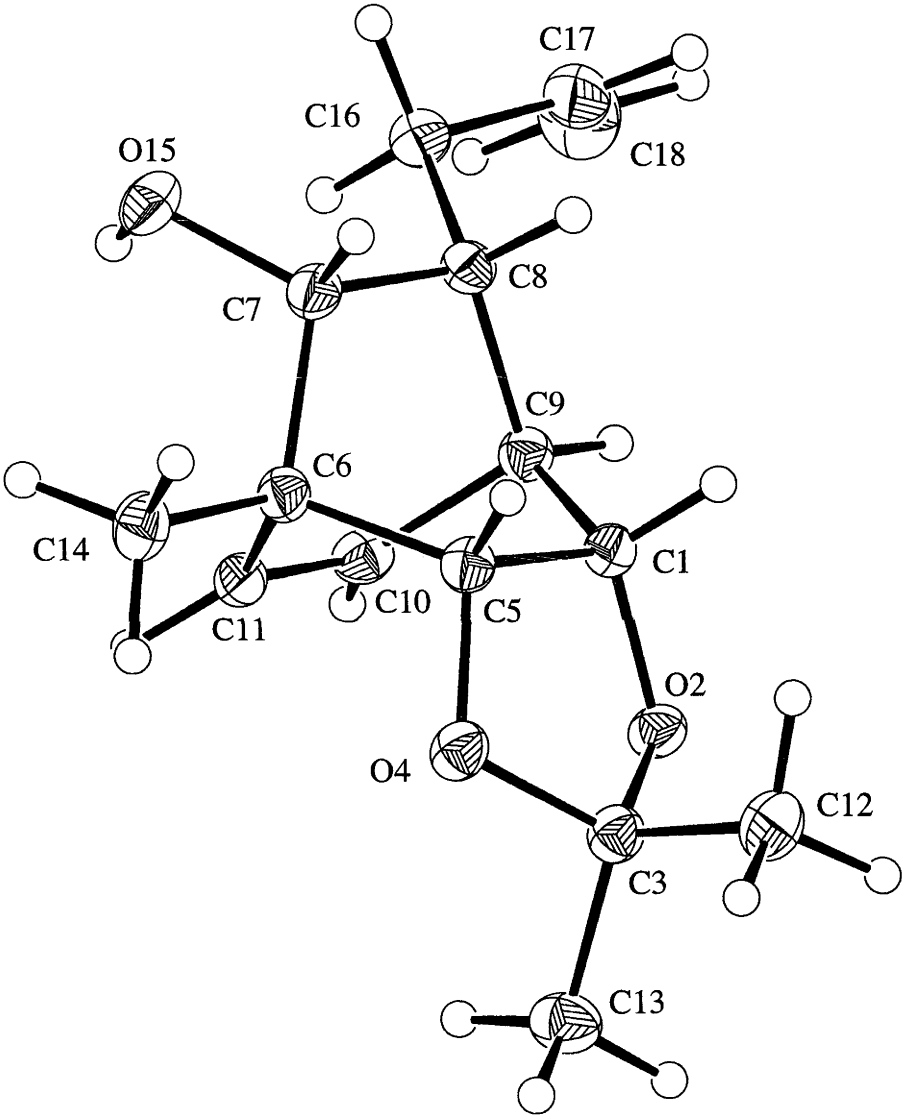
by

Anthony C. Willis

Research School of Chemistry, Institute of Advanced Studies

Australian National University, Canberra, ACT 0200, Australia

Thursday, 17th August, 2006


C17
C16
C18
O15
C8
C7
C9
C6
C14
C1
C10
C5
C11
O2
O4
C12
C3
C13

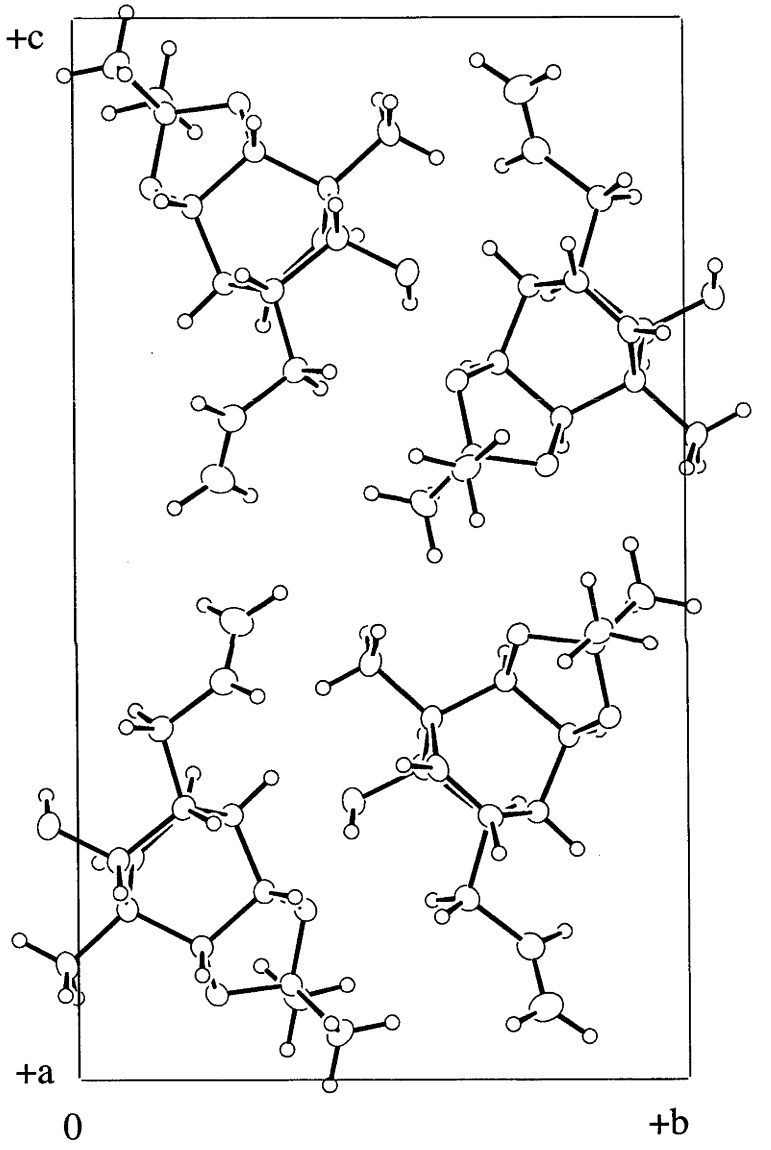

+c
+a
0
+b

Figure Captions for $C_{15}H_{22}O_3$

Figure 1. Molecular structure of $C_{15}H_{22}O_3$ with labelling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

Figure 2. Unit cell packing diagram of $C_{15}H_{22}O_3$ projected down the *a* axis. Hydrogen atoms are drawn as circles with small radii.

Assignment of Chiral Centres

C1	S	C5	R	C6	R	C7	R
C8	R	C9	S				

Calculated by PLATON.
Spek, A.L. (2001). PLATON - A Multipurpose Crystallographic Tool, Utrecht University, Utrecht, The Netherlands.

17 Aug 2006

Crystal structure of $C_{15}H_{22}O_3$ –ban0623

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Abstract

The crystal structure of $C_{15}H_{22}O_3$ is reported.

Comment

The compound is enantiometrically pure but the anomolous dispersion terms are very low for all elements in the structure and so the absolute configuration can not be determined in this experiment. Consequently Friedel-pair reflections have been averaged and the Flack parameter has not been refined. The absolute configuration of the molecule has been assigned on the basis of the synthetic precursors.

The crystallographic asymmetric unit consists of one molecule of $C_{15}H_{22}O_3$.

The final difference electron density map is essentially featureless, with the largest peaks being located between atoms.

Experimental

The compound was prepared by CD and recrystallized from hexane. The sample ID is 2CD83*p*40–53recryst.

Crystal data

$C_{15}H_{22}O_3$

$M_r = 250.34$

Orthorhombic

$P2_12_12_1$

$a = 6.3653\,(1)$ Å

$b = 11.2457\,(2)$ Å

$c = 19.6212\,(3)$ Å

$V = 1404.53\,(4)$ Å^3

$Z = 4$

$D_x = 1.184$ Mg m^{-3}

D_m not measured

Mo $K\alpha$ radiation

$\lambda = 0.71073$ Å

Cell parameters from 14317 reflections

$\theta = 3$–$27°$

$\mu = 0.081$ mm^{-1}

$T = 200$ K

Needle

Colourless

$0.44 \times 0.20 \times 0.14$ mm

Crystal source: local

Data collection

Nonius KappaCCD diffractometer

φ and ω scans with CCD

Absorption correction:

by integration *via* Gaussian method (Coppens, 1970) implemented in maXus (2000)

$T_{min} = 0.975$, $T_{max} = 0.991$

20591 measured reflections

1873 independent reflections

1495 reflections with

$I > 3.0\sigma(I)$

$R_{int} = 0.034$

$\theta_{max} = 27.477°$

$h = -8 \rightarrow 7$

$k = -14 \rightarrow 14$

$l = -25 \rightarrow 25$

Refinement

Refinement on F

$R = 0.0277$

$wR = 0.0337$

$S = 1.0987$

1495 reflections

166 parameters

H atoms treated by a mixture of independent and constrained refinement

Method, part 1, Chebychev polynomial, (Watkin, 1994, Prince, 1982) [weight] = $1.0/[A_0{*}T_0(x) + A_1{*}T_1(x) \ldots + A_{n-1}]{*}T_{n-1}(x)]$ where A_i are the Chebychev coefficients listed below and x= Fcalc/Fmax Method = Robust Weighting (Prince, 1982) W = [weight] * [1-(deltaF/6*sigmaF)^2]^2 A_i are: 0.768 0.278 0.503

$(\Delta/\sigma)_{max} = 0.000787$

$\Delta\rho_{max} = 0.15$ e Å^{-3}

$\Delta\rho_{min} = -0.12$ e Å^{-3}

Extinction correction: none

Scattering factors from International Tables Vol C 4.2.6.8 and 6.1.1.4

Absolute structure: The enantiomer has been assigned by reference to an unchanging chiral centre in the synthetic procedure.

Table 1. *Selected geometric parameters (Å, °)*

O2—C1	1.4370 (17)	C6—C7	1.553 (2)
O2—C3	1.4327 (17)	C6—C11	1.513 (2)
O4—C3	1.4262 (18)	C6—C14	1.528 (2)
O4—C5	1.4279 (19)	C7—C8	1.560 (2)
O15—C7	1.4301 (18)	C8—C9	1.553 (2)
C1—C5	1.5446 (19)	C8—C16	1.537 (2)
C1—C9	1.5326 (19)	C9—C10	1.505 (2)
C3—C12	1.523 (2)	C10—C11	1.325 (2)
C3—C13	1.510 (2)	C16—C17	1.497 (2)
C5—C6	1.5422 (19)	C17—C18	1.310 (3)

C1—O2—C3	106.59 (11)	C5—C6—C14	110.62 (12)
C3—O4—C5	107.76 (11)	C7—C6—C14	112.20 (12)
O2—C1—C5	104.13 (11)	C11—C6—C14	113.72 (13)
O2—C1—C9	111.80 (12)	C6—C7—O15	111.33 (12)
C5—C1—C9	109.00 (11)	C6—C7—C8	109.82 (12)
O2—C3—O4	104.67 (12)	O15—C7—C8	114.45 (12)
O2—C3—C12	110.05 (13)	C7—C8—C9	109.32 (12)
O4—C3—C12	110.71 (13)	C7—C8—C16	113.23 (12)
O2—C3—C13	109.31 (13)	C9—C8—C16	111.31 (12)
O4—C3—C13	107.85 (14)	C1—C9—C8	104.80 (12)
C12—C3—C13	113.83 (15)	C1—C9—C10	108.39 (12)
C1—C5—O4	104.82 (11)	C8—C9—C10	109.41 (11)
C1—C5—C6	111.28 (12)	C9—C10—C11	114.85 (13)
O4—C5—C6	110.29 (12)	C6—C11—C10	115.35 (13)
C5—C6—C7	104.82 (12)	C8—C16—C17	112.49 (13)
C5—C6—C11	108.41 (12)	C16—C17—C18	125.0 (2)
C7—C6—C11	106.59 (12)		

Table 2. *Hydrogen-bonding geometry (Å, °)*

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O15—H1···O2^{i}	0.86 (2)	2.14 (2)	2.954 (2)	158 (2)

Symmetry codes: (i) $1-x, y-\frac{1}{2}, \frac{1}{2}-z$.

The alcohol H atom was located in a difference electron density map and refined positionally. Other H atoms were added at calculated positions and, during refinement, each rides on the C atom to which it is attached.

Data collection: *COLLECT* (Nonius BV, 1997). Cell refinement: Denzo/Scalepack . Data reduction: Denzo/Scalepack (Otwinowski & Minor, 1997). Program(s) used to solve structure: *SIR*92 (Altomare *et al.* 1994). Program(s) used to refine structure: *CRYSTALS* (Watkin *et al.*2003). Molecular graphics: *ORTEP*–II (Johnson 1976) in teXsan (MSC, 1992–1997) . Software used to prepare material for publication: *CRYSTALS* .

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Supplementary data

Table *S*1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å²)*

$$U_{\rm eq} = (1/3)\Sigma_i\Sigma_j U^{ij} a^i a^j \mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	$U_{\rm eq}$
O2	0.52189 (17)	0.87209 (9)	0.34046 (5)	0.0318
O4	0.50856 (19)	0.72621 (9)	0.41979 (5)	0.0341
O15	0.1671 (2)	0.45237 (10)	0.26135 (6)	0.0387
C1	0.3372 (2)	0.80493 (12)	0.32337 (7)	0.0289
C3	0.5664 (3)	0.84769 (13)	0.41065 (7)	0.0318
C5	0.3358 (2)	0.70200 (12)	0.37549 (7)	0.0294
C6	0.3661 (2)	0.58081 (12)	0.34003 (8)	0.0298
C7	0.1693 (2)	0.56605 (13)	0.29400 (8)	0.0315
C8	0.1515 (2)	0.67383 (13)	0.24431 (8)	0.0305
C9	0.3503 (2)	0.75296 (12)	0.25129 (7)	0.0296
C10	0.5435 (2)	0.67622 (14)	0.24693 (8)	0.0319
C11	0.5533 (2)	0.58983 (13)	0.29275 (8)	0.0320
C12	0.4352 (3)	0.92815 (16)	0.45628 (9)	0.0457
C13	0.8001 (3)	0.85774 (17)	0.42268 (9)	0.0422
C14	0.3849 (3)	0.48129 (14)	0.39267 (9)	0.0403
C16	0.1147 (3)	0.63677 (15)	0.16989 (8)	0.0374
C17	0.0682 (3)	0.74066 (17)	0.12460 (9)	0.0458
C18	0.1669 (5)	0.7648 (2)	0.06765 (11)	0.0689
H1	0.269 (4)	0.4485 (17)	0.2329 (10)	0.0460
H11	0.2084 (2)	0.85503 (12)	0.32845 (7)	0.0346
H51	0.2013 (2)	0.70236 (12)	0.40182 (7)	0.0353
H71	0.0438 (2)	0.56902 (13)	0.32462 (8)	0.0378
H81	0.0279 (2)	0.72244 (13)	0.25899 (8)	0.0366
H91	0.3524 (2)	0.81716 (12)	0.21603 (7)	0.0355
H101	0.6559 (2)	0.68941 (14)	0.21213 (8)	0.0383
H111	0.6758 (2)	0.53444 (13)	0.29586 (8)	0.0384
H121	0.4673 (3)	0.91048 (16)	0.50513 (9)	0.0549
H122	0.4694 (3)	1.01317 (16)	0.44628 (9)	0.0549
H123	0.2826 (3)	0.91364 (16)	0.44739 (9)	0.0549
H131	0.8316 (3)	0.84074 (17)	0.47165 (9)	0.0506
H132	0.8478 (3)	0.94004 (17)	0.41114 (9)	0.0506
H133	0.8755 (3)	0.79911 (17)	0.39320 (9)	0.0506
H141	0.4044 (3)	0.40353 (14)	0.36877 (9)	0.0484
H142	0.5084 (3)	0.49690 (14)	0.42286 (9)	0.0484
H143	0.2541 (3)	0.47830 (14)	0.42084 (9)	0.0484
H161	0.2436 (3)	0.59582 (15)	0.15267 (8)	0.0449
H162	−0.0070 (3)	0.58056 (15)	0.16821 (8)	0.0449
H171	−0.0468 (3)	0.79583 (17)	0.13890 (9)	0.0550
H181	0.1262 (5)	0.8361 (2)	0.04027 (11)	0.0827
H182	0.2829 (5)	0.7118 (2)	0.05157 (11)	0.0827

Table *S*2. *Anisotropic displacement parameters* (Å²)

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O2	0.0349 (6)	0.0293 (5)	0.0311 (5)	−0.0059 (4)	−0.0043 (4)	0.0032 (4)
O4	0.0419 (6)	0.0296 (5)	0.0307 (5)	−0.0042 (5)	−0.0031 (5)	0.0035 (4)
O15	0.0418 (6)	0.0294 (5)	0.0448 (6)	−0.0094 (5)	0.0050 (6)	−0.0042 (5)
C1	0.0275 (7)	0.0256 (6)	0.0335 (7)	−0.0003 (6)	−0.0002 (6)	−0.0001 (5)
C3	0.0363 (8)	0.0291 (7)	0.0301 (7)	−0.0014 (6)	−0.0015 (6)	0.0017 (6)
C5	0.0289 (7)	0.0286 (6)	0.0308 (7)	−0.0012 (6)	0.0033 (6)	0.0005 (5)
C6	0.0274 (7)	0.0262 (6)	0.0358 (7)	−0.0011 (6)	0.0028 (6)	0.0015 (6)
C7	0.0264 (7)	0.0292 (7)	0.0389 (8)	−0.0023 (6)	0.0044 (6)	−0.0029 (6)
C8	0.0247 (6)	0.0317 (6)	0.0352 (7)	0.0011 (6)	0.0007 (6)	−0.0035 (6)
C9	0.0302 (7)	0.0285 (6)	0.0300 (6)	−0.0013 (6)	−0.0002 (6)	0.0010 (6)
C10	0.0268 (7)	0.0365 (7)	0.0324 (7)	−0.0040 (6)	0.0048 (6)	−0.0038 (6)
C11	0.0242 (6)	0.0289 (7)	0.0427 (8)	0.0007 (6)	0.0028 (6)	−0.0068 (6)
C12	0.0531 (10)	0.0415 (9)	0.0425 (9)	0.0021 (8)	0.0004 (8)	−0.0123 (7)

C13	0.0394 (9)	0.0469 (9)	0.0402 (8)	−0.0052 (8)	−0.0058 (7)	0.0096 (8)
C14	0.0486 (10)	0.0285 (7)	0.0438 (9)	−0.0007 (7)	0.0006 (7)	0.0058 (6)
C16	0.0373 (8)	0.0367 (7)	0.0383 (7)	0.0007 (7)	−0.0048 (6)	−0.0046 (7)
C17	0.0496 (10)	0.0447 (9)	0.0432 (8)	0.0050 (8)	−0.0135 (8)	−0.0027 (8)
C18	0.0904 (18)	0.0674 (13)	0.0489 (11)	0.0079 (14)	−0.0052 (13)	0.0099 (10)

Table *S3. Geometric parameters (Å, °)*

O2—C1	1.4370 (17)	C9—C10	1.505 (2)
O2—C3	1.4327 (17)	C9—H91	1.000
O4—C3	1.4262 (18)	C10—C11	1.325 (2)
O4—C5	1.4279 (19)	C10—H101	1.000
O15—C7	1.4301 (18)	C11—H111	1.000
O15—H1	0.86 (2)	C12—H121	1.000
C1—C5	1.5446 (19)	C12—H122	1.000
C1—C9	1.5326 (19)	C12—H123	1.000
C1—H11	1.000	C13—H131	1.000
C3—C12	1.523 (2)	C13—H132	1.000
C3—C13	1.510 (2)	C13—H133	1.000
C5—C6	1.5422 (19)	C14—H141	1.000
C5—H51	1.000	C14—H142	1.000
C6—C7	1.553 (2)	C14—H143	1.000
C6—C11	1.513 (2)	C16—C17	1.497 (2)
C6—C14	1.528 (2)	C16—H161	1.000
C7—C8	1.560 (2)	C16—H162	1.000
C7—H71	1.000	C17—C18	1.310 (3)
C8—C9	1.553 (2)	C17—H171	1.000
C8—C16	1.537 (2)	C18—H181	1.000
C8—H81	1.000	C18—H182	1.000
C1—O2—C3	106.59 (11)	C8—C9—C10	109.41 (11)
C3—O4—C5	107.76 (11)	C1—C9—H91	111.3
C7—O15—H1	109.3 (14)	C8—C9—H91	111.3
O2—C1—C5	104.13 (11)	C10—C9—H91	111.3
O2—C1—C9	111.80 (12)	C9—C10—C11	114.85 (13)
C5—C1—C9	109.00 (11)	C9—C10—H101	122.6
O2—C1—H11	110.6	C11—C10—H101	122.6
C5—C1—H11	110.6	C6—C11—C10	115.35 (13)
C9—C1—H11	110.6	C6—C11—H111	122.3
O2—C3—O4	104.67 (12)	C10—C11—H111	122.3
O2—C3—C12	110.05 (13)	C3—C12—H121	109.5
O4—C3—C12	110.71 (13)	C3—C12—H122	109.5
O2—C3—C13	109.31 (13)	H121—C12—H122	109.5
O4—C3—C13	107.85 (14)	C3—C12—H123	109.5
C12—C3—C13	113.83 (15)	H121—C12—H123	109.5
C1—C5—O4	104.82 (11)	H122—C12—H123	109.5
C1—C5—C6	111.28 (12)	C3—C13—H131	109.5
O4—C5—C6	110.29 (12)	C3—C13—H132	109.5
C1—C5—H51	110.1	H131—C13—H132	109.5
O4—C5—H51	110.1	C3—C13—H133	109.5
C6—C5—H51	110.1	H131—C13—H133	109.5
C5—C6—C7	104.82 (12)	H132—C13—H133	109.5
C5—C6—C11	108.41 (12)	C6—C14—H141	109.5
C7—C6—C11	106.59 (12)	C6—C14—H142	109.5
C5—C6—C14	110.62 (12)	H141—C14—H142	109.5
C7—C6—C14	112.20 (12)	C6—C14—H143	109.5
C11—C6—C14	113.72 (13)	H141—C14—H143	109.5
C6—C7—O15	111.33 (12)	H142—C14—H143	109.5
C6—C7—C8	109.82 (12)	C8—C16—C17	112.49 (13)
O15—C7—C8	114.45 (12)	C8—C16—H161	108.7
C6—C7—H71	106.9	C17—C16—H161	108.7
O15—C7—H71	106.9	C8—C16—H162	108.7
C8—C7—H71	106.9	C17—C16—H162	108.7
C7—C8—C9	109.32 (12)	H161—C16—H162	109.5
C7—C8—C16	113.23 (12)	C16—C17—C18	125.0 (2)
C9—C8—C16	111.31 (12)	C16—C17—H171	117.5
C7—C8—H81	107.6	C18—C17—H171	117.5
C9—C8—H81	107.6	C17—C18—H181	120.0
C16—C8—H81	107.6	C17—C18—H182	120.0
C1—C9—C8	104.80 (12)	H181—C18—H182	120.0
C1—C9—C10	108.39 (12)		

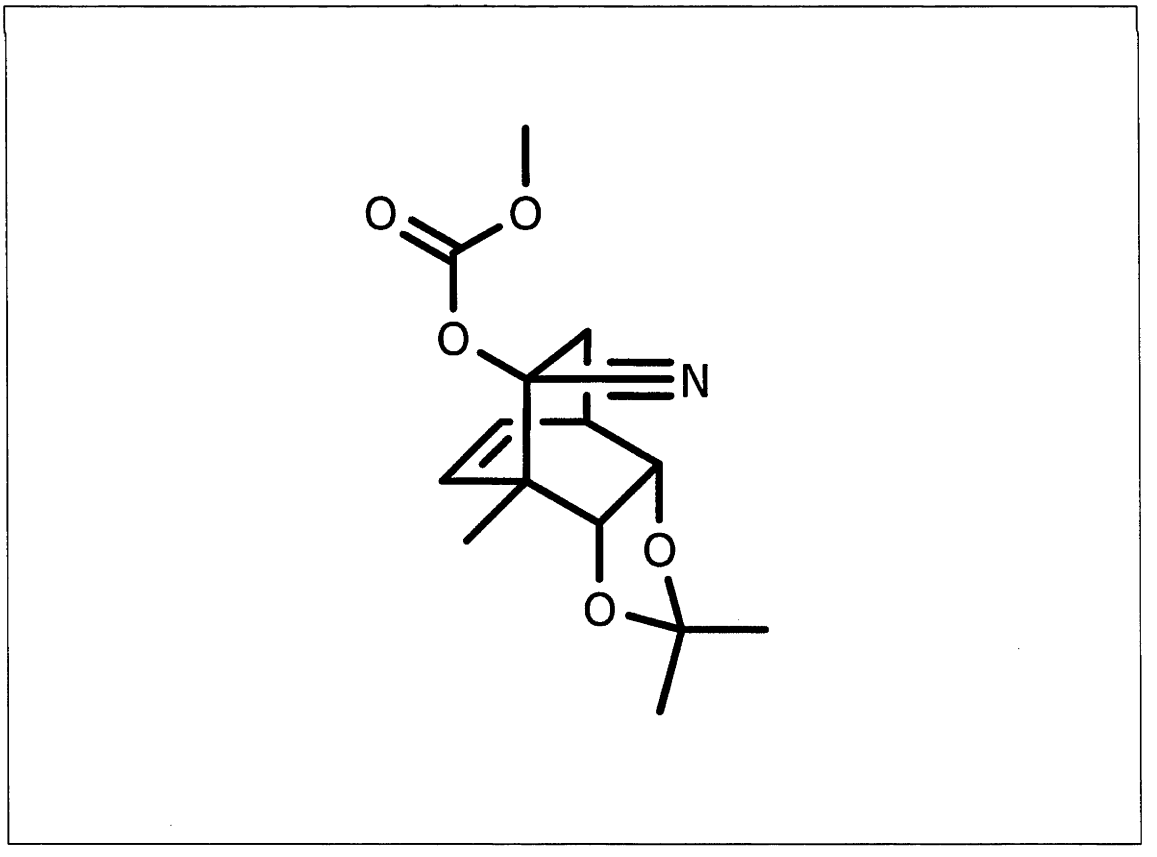
O2—C1—C5—O4	4.4 (1)	C3—O2—C1—C5	−24.1 (1)
O2—C1—C5—C6	−114.8 (1)	C3—O2—C1—C9	−141.6 (1)
O2—C1—C9—C8	174.4 (1)	C3—O4—C5—C6	136.8 (1)
O2—C1—C9—C10	57.7 (1)	C5—O4—C3—C12	86.2 (1)
O2—C3—O4—C5	−32.4 (2)	C5—O4—C3—C13	−148.7 (1)
O4—C3—O2—C1	35.2 (1)	C5—C1—C9—C8	59.9 (1)
O4—C5—C1—C9	123.9 (1)	C5—C1—C9—C10	−56.9 (1)
O4—C5—C6—C7	180.0 (1)	C5—C6—C7—C8	56.6 (1)
O4—C5—C6—C11	−66.5 (1)	C5—C6—C11—C10	−55.7 (2)
O4—C5—C6—C14	58.8 (1)	C6—C5—C1—C9	4.7 (1)
O15—C7—C6—C5	−175.6 (1)	C6—C7—C8—C9	6.6 (2)
O15—C7—C6—C11	69.6 (1)	C6—C7—C8—C16	131.3 (1)
O15—C7—C6—C14	−55.5 (2)	C6—C11—C10—C9	1.8 (2)
O15—C7—C8—C9	−119.5 (1)	C7—C6—C11—C10	56.6 (2)
O15—C7—C8—C16	5.2 (2)	C7—C8—C9—C10	49.4 (2)
C1—O2—C3—C12	−83.8 (1)	C7—C8—C16—C17	172.0 (1)
C1—O2—C3—C13	150.5 (1)	C8—C7—C6—C11	−58.2 (1)
C1—C5—O4—C3	17.0 (1)	C8—C7—C6—C14	176.7 (1)
C1—C5—C6—C7	−64.1 (1)	C8—C9—C10—C11	−57.4 (2)
C1—C5—C6—C11	49.4 (1)	C8—C16—C17—C18	127.6 (2)
C1—C5—C6—C14	174.7 (1)	C9—C8—C16—C17	−64.3 (2)
C1—C9—C8—C7	−66.7 (1)	C10—C9—C8—C16	−76.5 (1)
C1—C9—C8—C16	167.5 (1)	C10—C11—C6—C14	−179.2 (1)
C1—C9—C10—C11	56.4 (2)		

Table *S4. Contact distances (Å)*

O2···O15^{i}	2.954 (2)	O15···C17^{iii}	3.594 (2)
O4···C13^{ii}	3.494 (2)		

Symmetry codes: (i) $1-x, \frac{1}{2}+y, \frac{1}{2}-z$; (ii) $x-\frac{1}{2}, \frac{3}{2}-y, 1-z$; (iii) $-x, y-\frac{1}{2}, \frac{1}{2}-z$.

A.4 X-ray crystal structure report for compound 152b



Sample: ban0631

Compound: $C_{15}H_{19}NO_5$

X-ray Structure Report

for

Christine Dietinger and Martin G. Banwell

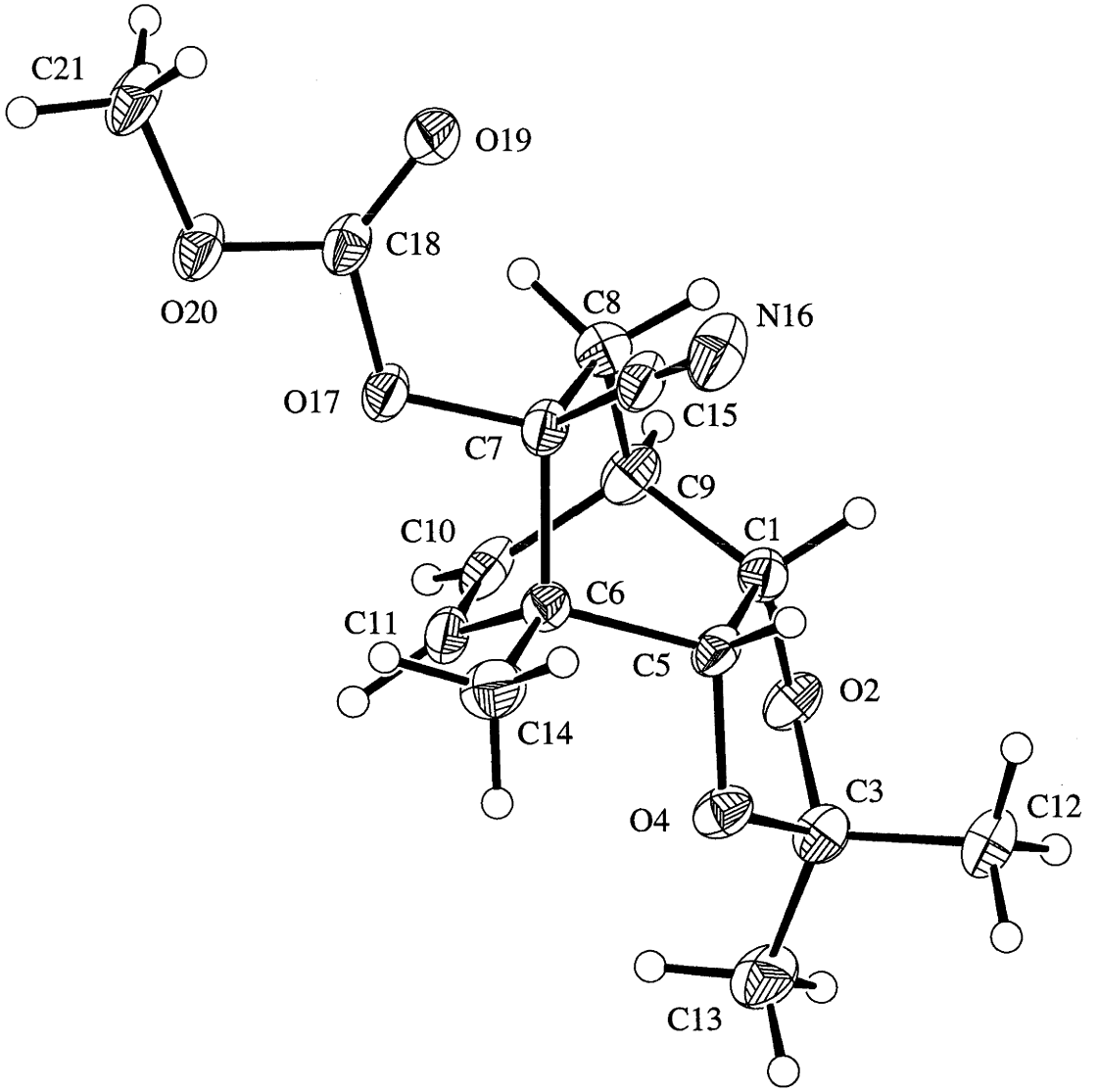
by

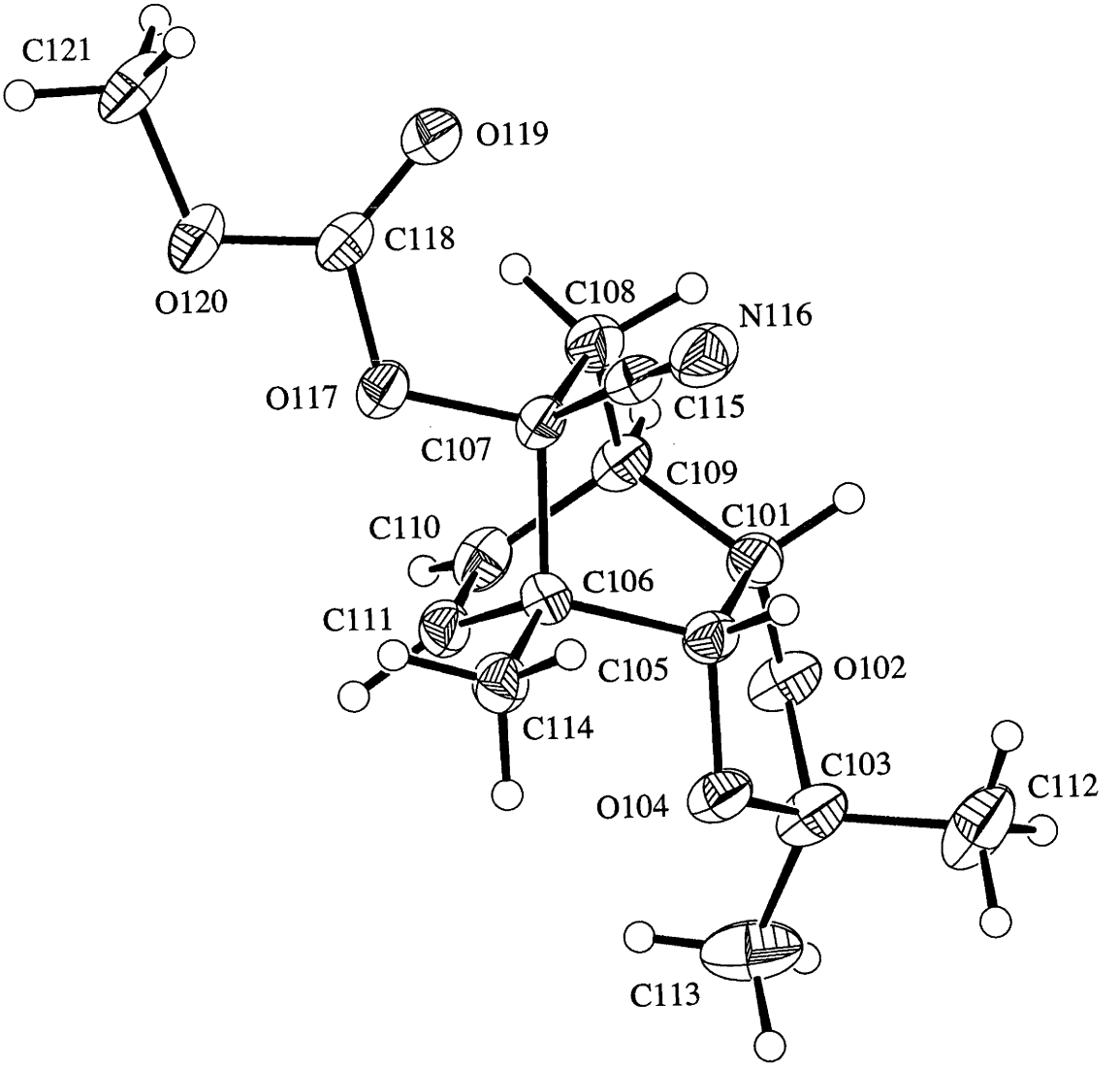
Anthony C. Willis

Research School of Chemistry,

The Australian National University, Canberra, ACT 0200, Australia

Tuesday, 3rd October, 2006


C21
O19
C18
O20
C8
N16
O17
C15
C7
C9
C10
C1
C6
C11
C5
O2
C14
C3
C12
O4
C13


C121
O119
C118
O120
C108
N116
O117
C115
C107
C109
C110
C101
C106
C111
C105
O102
C114
C103
O104
C112
C113

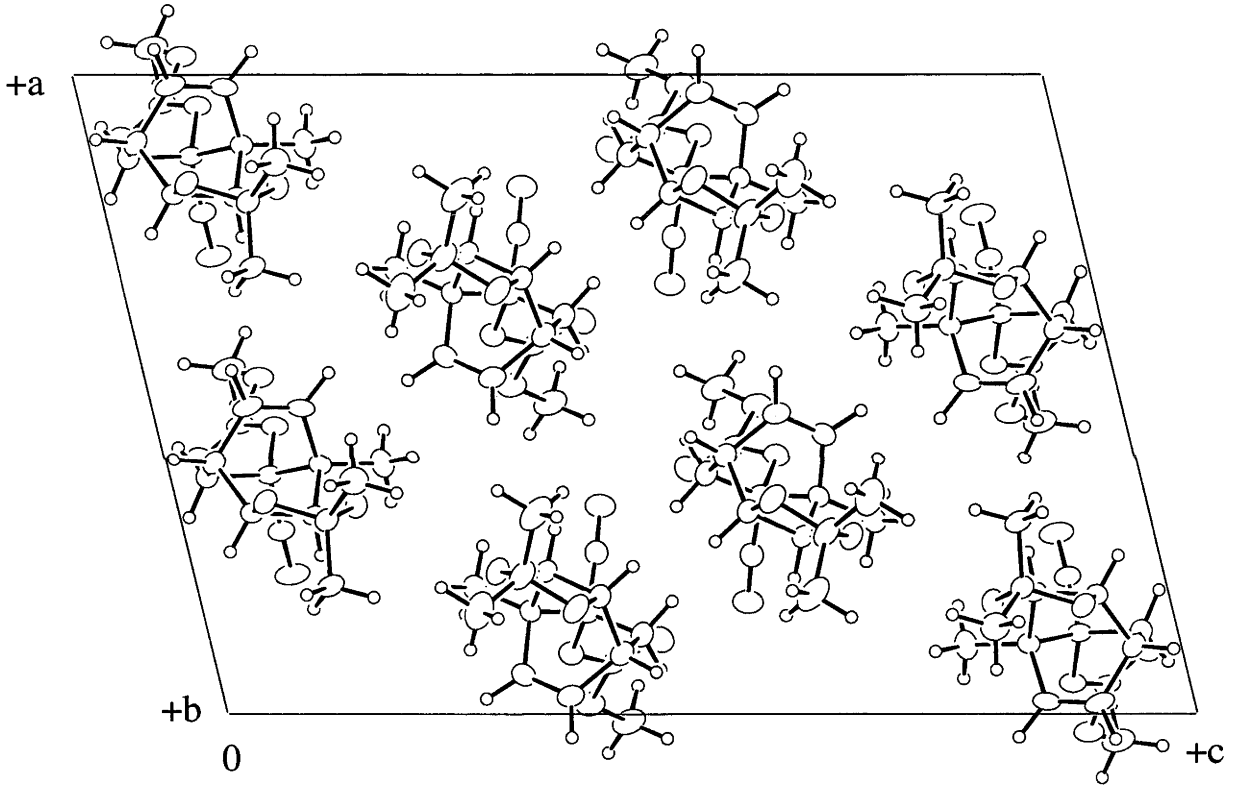

+a
+b
0
+c

Figure Captions for $C_{15}H_{19}NO_5$

Figure 1. Molecule one of $C_{15}H_{19}NO_5$ with labelling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

Figure 2. Molecule two of $C_{15}H_{19}NO_5$ with labelling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

Figure 3. Unit cell packing diagram of $C_{15}H_{19}NO_5$ projected down the *b* axis. Hydrogen atoms are drawn as circles with small radii.

Assignment of Chiral Centres

C1	S		C5	R		C6	S		C7	R		C9	R
C101	S		C105	R		C106	S		C107	R		C109	R

Calculated by PLATON.
Spek, A.L. (2001). PLATON - A Multipurpose Crystallographic Tool, Utrecht University, Utrecht, The Netherlands.

3 Oct 2006

Crystal structure of $C_{15}H_{19}NO_5$ –ban0631

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Abstract

The crystal structure of $C_{15}H_{19}NO_5$ is reported.

Comment

The compound is enantiometrically pure but the anomolous dispersion terms are very low for all elements in the structure and so the absolute configuration can not be determined in this experiment. Consequently Friedel-pair reflections have been averaged and the Flack parameter has not been refined. The absolute configuration of the molecule has been assigned on the basis of the synthetic precursors.

The crystallographic asymmetric unit consists of two molecules of $C_{15}H_{19}NO_5$.

The crystals supplied were very thin and fragile and gave a diffraction pattern of indifferent quality. During data collection, spots were observed that did not belong to the major diffraction pattern, suggesting that the crystal was fractured or was twinned to some degree. The structure was initially solved and refined assuming that there was no twinning and yielded an *R*-factor for unit weights of 0.075. A possible twin rule were identified using ROTAX within *CRYSTALS* (a rotation of 180° about direct vector 0 0 1), and when this twinning was included in the refinement to allow for overlapping reflections the *R*-factor lowered to 0.049 for the same stage of refinement. The final twin ratio was 0.872:0.128(2)

The final difference electron density map is essentially featureless, with the largest peaks being located near H atoms.

Experimental

The compound was prepared by CD and recrystallized from hexane/benzene. The sample ID is 3CD16*p*32–48.

Crystal data

$C_{15}H_{19}NO_5$
$M_r = 293.32$
Monoclinic
$C2$
$a = 14.6704\,(4)$ Å
$b = 9.7540\,(3)$ Å
$c = 21.5432\,(6)$ Å
$\beta = 103.3248\,(13)°$
$V = 2999.74\,(15)$ Å^3
$Z = 8$
$D_x = 1.299$ Mg m^{-3}
D_m not measured
Mo $K\alpha$ radiation
$\lambda = 0.71073$ Å

Cell parameters from 79013 reflections
$\theta = 3$–$25°$
$\mu = 0.098$ mm^{-1}
$T = 200$ K
Needle
Colourless
$0.43 \times 0.19 \times 0.08$ mm
Crystal source: local

Data collection

Nonius KappaCCD diffractometer
φ and ω scans with CCD
Absorption correction:
multi-scan Denzo/Scalepack (Otwinowski & Minor, 1997)
$T_{min} = 0.89$, $T_{max} = 0.99$
24198 measured reflections
2822 independent reflections

2386 reflections with
$I > 1.5\sigma(I)$
$R_{int} = 0.060$
$\theta_{max} = 25.0°$
$h = -17 \rightarrow 17$
$k = -11 \rightarrow 10$
$l = -25 \rightarrow 25$

Refinement

Refinement on F

$R = 0.0475$

$wR = 0.0366$

$S = 1.1324$

2386 reflections

380 parameters

H-atom parameters not refined

Method, part 1, Chebychev polynomial, (Carruthers & Watkin, 1979, Prince, 1982) [weight] = $1.0/[A_0{*}T_0(x) + A_1{*}T_1(x) \ldots + A_{n-1}]{*}T_{n-1}(x)]$ where A_i are the Chebychev coefficients listed below and x= Fcalc/Fmax Method = Robust Weighting (Prince, 1982) W = [weight] * [1-(deltaF/6*sigmaF)^2]^2 A_i are: 0.725 0.123 0.619 0.0715 0.137

$(\Delta/\sigma)_{\max} = 0.000441$

$\Delta\rho_{\max} = 0.19$ e Å^{-3}

$\Delta\rho_{\min} = -0.16$ e Å^{-3}

Extinction correction: none

Scattering factors from International Tables Vol C 4.2.6.8 and 6.1.1.4

Absolute structure: The enantiomer has been assigned by reference to an unchanging chiral centre in the synthetic procedure.

Table 1. *Selected geometric parameters (Å, °)*

O2—C1	1.442 (4)	C3—C13	1.516 (5)
O2—C3	1.431 (4)	C5—C6	1.556 (5)
O4—C3	1.433 (4)	C6—C7	1.562 (5)
O4—C5	1.422 (4)	C6—C11	1.505 (5)
O17—C7	1.442 (4)	C6—C14	1.519 (5)
O17—C18	1.355 (4)	C7—C8	1.544 (5)
O19—C18	1.190 (4)	C7—C15	1.490 (5)
O20—C18	1.319 (4)	C8—C9	1.550 (5)
O20—C21	1.460 (4)	C9—C10	1.489 (5)
O102—C101	1.418 (5)	C10—C11	1.315 (5)
O102—C103	1.424 (5)	C101—C105	1.543 (5)
O104—C103	1.425 (5)	C101—C109	1.525 (5)
O104—C105	1.425 (4)	C103—C112	1.509 (6)
O117—C107	1.450 (4)	C103—C113	1.506 (6)
O117—C118	1.352 (4)	C105—C106	1.535 (5)
O119—C118	1.196 (4)	C106—C107	1.569 (5)
O120—C118	1.313 (4)	C106—C111	1.509 (5)
O120—C121	1.452 (5)	C106—C114	1.531 (5)
N16—C15	1.143 (4)	C107—C108	1.541 (5)
N116—C115	1.142 (5)	C107—C115	1.483 (5)
C1—C5	1.540 (5)	C108—C109	1.540 (6)
C1—C9	1.521 (5)	C109—C110	1.495 (5)
C3—C12	1.503 (5)	C110—C111	1.323 (5)

C1—O2—C3	106.9 (2)	C7—C15—N16	177.2 (4)
C3—O4—C5	107.3 (2)	O17—C18—O20	105.9 (3)
C7—O17—C18	118.6 (3)	O17—C18—O19	125.4 (3)
C18—O20—C21	115.1 (3)	O20—C18—O19	128.7 (3)
C101—O102—C103	108.4 (3)	O102—C101—C105	104.3 (3)
C103—O104—C105	108.1 (3)	O102—C101—C109	111.6 (3)
C107—O117—C118	117.3 (3)	C105—C101—C109	108.5 (3)
C118—O120—C121	114.8 (3)	O104—C103—O102	104.3 (3)
O2—C1—C5	104.2 (3)	O104—C103—C112	110.5 (4)
O2—C1—C9	110.8 (3)	O102—C103—C112	110.4 (4)
C5—C1—C9	109.7 (3)	O104—C103—C113	108.0 (4)
O4—C3—O2	104.4 (3)	O102—C103—C113	108.7 (4)
O4—C3—C12	111.2 (3)	C112—C103—C113	114.4 (4)
O2—C3—C12	110.9 (3)	C101—C105—O104	104.5 (3)
O4—C3—C13	107.5 (3)	C101—C105—C106	111.7 (3)
O2—C3—C13	108.7 (3)	O104—C105—C106	109.0 (3)
C12—C3—C13	113.7 (3)	C105—C106—C107	106.2 (3)
C1—C5—O4	105.0 (3)	C105—C106—C111	107.9 (3)
C1—C5—C6	110.8 (3)	C107—C106—C111	105.2 (3)
O4—C5—C6	108.9 (3)	C105—C106—C114	111.0 (3)
C5—C6—C7	105.9 (3)	C107—C106—C114	112.1 (3)
C5—C6—C11	107.3 (3)	C111—C106—C114	114.0 (3)
C7—C6—C11	104.5 (3)	C106—C107—O117	104.2 (3)
C5—C6—C14	111.8 (3)	C106—C107—C108	109.6 (3)
C7—C6—C14	112.9 (3)	O117—C107—C108	112.5 (3)
C11—C6—C14	113.9 (3)	C106—C107—C115	109.8 (3)
C6—C7—O17	103.3 (3)	O117—C107—C115	107.6 (3)
C6—C7—C8	110.4 (3)	C108—C107—C115	112.7 (3)
O17—C7—C8	113.3 (3)	C107—C108—C109	109.9 (3)
C6—C7—C15	110.4 (3)	C108—C109—C101	106.3 (3)
O17—C7—C15	108.1 (3)	C108—C109—C110	108.3 (3)
C8—C7—C15	111.1 (3)	C101—C109—C110	108.9 (3)
C7—C8—C9	109.4 (3)	C109—C110—C111	115.0 (4)
C8—C9—C1	106.0 (3)	C106—C111—C110	115.1 (3)
C8—C9—C10	107.9 (3)	C107—C115—N116	176.2 (4)
C1—C9—C10	109.3 (3)	O117—C118—O120	106.4 (3)
C9—C10—C11	114.3 (3)	O117—C118—O119	125.9 (3)
C6—C11—C10	116.8 (3)	O120—C118—O119	127.6 (4)

H atoms were added at calculated positions and, during refinement, each rides on the C atom to which it is attached.

Data collection: *COLLECT* (Nonius BV, 1997). Cell refinement: Denzo/Scalepack (Otwinowski & Minor, 1997). Data reduction: Denzo/Scalepack (Otwinowski & Minor, 1997). Program(s) used to solve structure: *SIR*92 (Altomare *et al.* 1994). Program(s) used to refine structure: *CRYSTALS* (Watkin *et al.*2003). Molecular graphics: *ORTEP*–II (Johnson 1976) in teXsan (MSC, 1992–1997) . Software used to prepare material for publication: *CRYSTALS* (Watkin *et al.*2003).

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Supplementary data

Table S1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å²)*

$$U_{\mathrm{eq}} = (1/3)\Sigma_i\Sigma_j U^{ij} a^i a^j \mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	U_{eq}
O2	0.33129 (17)	0.8594 (2)	0.09140 (11)	0.0402
O4	0.32508 (17)	0.7545 (2)	0.18399 (11)	0.0398
O17	0.45168 (16)	0.3391 (2)	0.12165 (12)	0.0411
O19	0.40018 (18)	0.1973 (3)	0.03775 (14)	0.0530
O20	0.52792 (16)	0.1546 (2)	0.11688 (13)	0.0477
O102	0.6641 (2)	1.1028 (3)	0.38495 (13)	0.0551
O104	0.72265 (18)	0.9846 (3)	0.31325 (12)	0.0476
O117	0.59439 (17)	0.5629 (3)	0.36887 (12)	0.0463
O119	0.61633 (19)	0.4558 (3)	0.46475 (14)	0.0579
O120	0.51564 (18)	0.3818 (3)	0.37580 (13)	0.0546
N16	0.2178 (2)	0.2976 (3)	0.10108 (19)	0.0595
N116	0.8253 (2)	0.5646 (4)	0.43576 (17)	0.0633
C1	0.3139 (2)	0.7171 (3)	0.07467 (16)	0.0368
C3	0.3029 (2)	0.8808 (4)	0.14991 (17)	0.0393
C5	0.3103 (2)	0.6471 (3)	0.13812 (17)	0.0339
C6	0.3906 (2)	0.5401 (4)	0.15735 (16)	0.0358
C7	0.3738 (2)	0.4320 (4)	0.10238 (16)	0.0372
C8	0.3709 (3)	0.5026 (4)	0.03782 (17)	0.0442
C9	0.3937 (3)	0.6570 (4)	0.04905 (18)	0.0433
C10	0.4826 (2)	0.6685 (4)	0.0987 (2)	0.0469
C11	0.4804 (2)	0.6102 (4)	0.15334 (19)	0.0432
C12	0.1999 (2)	0.9114 (4)	0.13751 (19)	0.0481
C13	0.3643 (3)	0.9914 (4)	0.1877 (2)	0.0553
C14	0.3927 (3)	0.4769 (4)	0.22212 (17)	0.0550
C15	0.2859 (3)	0.3540 (4)	0.10058 (18)	0.0428
C18	0.4542 (2)	0.2246 (3)	0.0865 (2)	0.0396
C21	0.5416 (3)	0.0226 (4)	0.0885 (2)	0.0537
C101	0.6836 (3)	0.9712 (4)	0.41282 (17)	0.0438
C103	0.7167 (3)	1.1194 (4)	0.3376 (2)	0.0566
C105	0.7231 (2)	0.8896 (4)	0.36352 (16)	0.0418
C106	0.6603 (2)	0.7672 (4)	0.33697 (16)	0.0399
C107	0.6583 (2)	0.6725 (4)	0.39552 (17)	0.0418
C108	0.6241 (3)	0.7553 (4)	0.44668 (18)	0.0506
C109	0.5947 (3)	0.9002 (4)	0.42147 (18)	0.0457
C110	0.5281 (3)	0.8868 (4)	0.35779 (19)	0.0496
C111	0.5613 (3)	0.8193 (4)	0.31445 (18)	0.0430
C112	0.8132 (3)	1.1739 (5)	0.3672 (2)	0.0851
C113	0.6611 (4)	1.2065 (5)	0.2844 (2)	0.0853
C114	0.6975 (3)	0.6921 (4)	0.28550 (18)	0.0470
C115	0.7520 (3)	0.6107 (4)	0.42008 (17)	0.0455
C118	0.5791 (3)	0.4641 (4)	0.4093 (2)	0.0439
C121	0.4883 (3)	0.2690 (4)	0.4115 (2)	0.0630
H11	0.2529 (2)	0.7063 (3)	0.04284 (16)	0.0435
H51	0.2479 (2)	0.6030 (3)	0.13513 (17)	0.0409
H81	0.4183 (3)	0.4592 (4)	0.01728 (17)	0.0528
H82	0.3070 (3)	0.4921 (4)	0.00930 (17)	0.0528
H91	0.3989 (3)	0.7034 (4)	0.00862 (18)	0.0537
H101	0.5392 (2)	0.7169 (4)	0.0911 (2)	0.0586
H111	0.5358 (2)	0.6121 (4)	0.19038 (19)	0.0501
H121	0.1817 (2)	0.9262 (4)	0.17897 (19)	0.0598
H122	0.1855 (2)	0.9958 (4)	0.11069 (19)	0.0598
H123	0.1639 (2)	0.8322 (4)	0.11456 (19)	0.0598
H131	0.3452 (3)	1.0074 (4)	0.2288 (2)	0.0652
H132	0.3567 (3)	1.0782 (4)	0.1623 (2)	0.0652
H133	0.4313 (3)	0.9617 (4)	0.1969 (2)	0.0652
H141	0.4449 (3)	0.4088 (4)	0.23280 (17)	0.0652
H142	0.4027 (3)	0.5505 (4)	0.25528 (17)	0.0652

H143	0.3318 (3)	0.4297 (4)	0.22091 (17)	0.0652
H211	0.5988 (3)	−0.0229 (4)	0.1146 (2)	0.0664
H212	0.5496 (3)	0.0372 (4)	0.0441 (2)	0.0664
H213	0.4858 (3)	−0.0371 (4)	0.0872 (2)	0.0664
H1011	0.7309 (3)	0.9773 (4)	0.45437 (17)	0.0525
H1051	0.7884 (2)	0.8581 (4)	0.38265 (16)	0.0506
H1081	0.6759 (3)	0.7626 (4)	0.48588 (18)	0.0612
H1082	0.5694 (3)	0.7075 (4)	0.45734 (18)	0.0612
H1091	0.5655 (3)	0.9520 (4)	0.45198 (18)	0.0566
H1101	0.4635 (3)	0.9263 (4)	0.34854 (19)	0.0601
H1111	0.5236 (3)	0.8041 (4)	0.27004 (18)	0.0496
H1121	0.8493 (3)	1.1852 (5)	0.3333 (2)	0.1102
H1122	0.8079 (3)	1.2645 (5)	0.3877 (2)	0.1102
H1123	0.8466 (3)	1.1076 (5)	0.4001 (2)	0.1102
H1131	0.6973 (4)	1.2190 (5)	0.2508 (2)	0.1085
H1132	0.6486 (4)	1.2980 (5)	0.3017 (2)	0.1085
H1133	0.6002 (4)	1.1601 (5)	0.2655 (2)	0.1085
H1141	0.6556 (3)	0.6129 (4)	0.26903 (18)	0.0561
H1142	0.7623 (3)	0.6577 (4)	0.30419 (18)	0.0561
H1143	0.6991 (3)	0.7566 (4)	0.24967 (18)	0.0561
H1211	0.4398 (3)	0.2120 (4)	0.3825 (2)	0.0777
H1212	0.5443 (3)	0.2111 (4)	0.4297 (2)	0.0777
H1213	0.4618 (3)	0.3060 (4)	0.4469 (2)	0.0777

Table *S2. Anisotropic displacement parameters* (Å^2)

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O2	0.0489 (15)	0.0263 (13)	0.0511 (14)	0.0051 (11)	0.0229 (12)	0.0040 (12)
O4	0.0523 (15)	0.0276 (13)	0.0418 (14)	0.0054 (11)	0.0155 (12)	0.0009 (11)
O17	0.0309 (13)	0.0310 (13)	0.0594 (16)	0.0051 (11)	0.0064 (11)	−0.0063 (12)
O19	0.0460 (15)	0.0428 (16)	0.0639 (17)	0.0102 (13)	−0.0001 (13)	−0.0155 (14)
O20	0.0357 (14)	0.0284 (14)	0.0782 (18)	0.0056 (11)	0.0114 (13)	−0.0019 (14)
O102	0.0699 (19)	0.0389 (15)	0.0679 (19)	−0.0021 (14)	0.0393 (16)	0.0001 (14)
O104	0.0628 (17)	0.0356 (15)	0.0507 (15)	−0.0064 (13)	0.0264 (13)	−0.0005 (13)
O117	0.0444 (14)	0.0402 (15)	0.0528 (16)	−0.0112 (12)	0.0081 (12)	0.0021 (13)
O119	0.0565 (17)	0.0577 (18)	0.0560 (17)	−0.0150 (15)	0.0060 (14)	0.0154 (15)
O120	0.0471 (16)	0.0405 (15)	0.0762 (19)	−0.0134 (14)	0.0144 (14)	0.0001 (15)
N16	0.0386 (19)	0.0368 (18)	0.106 (3)	−0.0035 (16)	0.0219 (19)	−0.002 (2)
N116	0.046 (2)	0.066 (2)	0.076 (2)	−0.0021 (19)	0.0090 (18)	0.023 (2)
C1	0.0336 (18)	0.034 (2)	0.0415 (19)	0.0015 (16)	0.0065 (15)	0.0004 (16)
C3	0.044 (2)	0.0293 (18)	0.048 (2)	0.0017 (17)	0.0157 (17)	0.0052 (17)
C5	0.0319 (18)	0.0252 (17)	0.0465 (19)	0.0021 (15)	0.0130 (15)	−0.0031 (16)
C6	0.0353 (18)	0.0287 (18)	0.042 (2)	0.0039 (15)	0.0064 (15)	−0.0031 (17)
C7	0.0279 (17)	0.0327 (19)	0.051 (2)	0.0023 (15)	0.0084 (15)	−0.0020 (18)
C8	0.043 (2)	0.048 (2)	0.041 (2)	0.0041 (18)	0.0105 (17)	−0.0042 (18)
C9	0.049 (2)	0.038 (2)	0.049 (2)	0.0053 (18)	0.0234 (18)	0.0053 (18)
C10	0.035 (2)	0.0285 (19)	0.083 (3)	0.0017 (16)	0.026 (2)	−0.008 (2)
C11	0.0259 (18)	0.038 (2)	0.062 (2)	0.0060 (16)	0.0024 (17)	−0.011 (2)
C12	0.042 (2)	0.041 (2)	0.067 (2)	0.0092 (18)	0.0237 (18)	0.007 (2)
C13	0.065 (3)	0.028 (2)	0.074 (3)	0.0024 (19)	0.018 (2)	−0.004 (2)
C14	0.074 (3)	0.046 (2)	0.043 (2)	0.016 (2)	0.010 (2)	0.004 (2)
C15	0.034 (2)	0.033 (2)	0.061 (2)	0.0066 (17)	0.0128 (17)	−0.0020 (19)
C18	0.0283 (18)	0.0283 (19)	0.064 (2)	−0.0002 (16)	0.0133 (18)	−0.0019 (19)
C21	0.044 (2)	0.0252 (19)	0.096 (3)	0.0073 (17)	0.024 (2)	−0.001 (2)
C101	0.047 (2)	0.044 (2)	0.042 (2)	−0.0050 (18)	0.0146 (17)	−0.0044 (19)
C103	0.071 (3)	0.041 (2)	0.069 (3)	−0.008 (2)	0.040 (2)	−0.006 (2)
C105	0.042 (2)	0.045 (2)	0.0408 (19)	−0.0051 (18)	0.0157 (16)	−0.0007 (19)
C106	0.0389 (19)	0.043 (2)	0.0361 (19)	−0.0039 (18)	0.0050 (16)	0.0004 (17)
C107	0.037 (2)	0.042 (2)	0.046 (2)	−0.0099 (17)	0.0071 (17)	0.0047 (19)
C108	0.053 (2)	0.057 (3)	0.045 (2)	−0.012 (2)	0.0176 (19)	−0.003 (2)
C109	0.050 (2)	0.040 (2)	0.052 (2)	−0.0056 (18)	0.0218 (18)	−0.0021 (19)
C110	0.039 (2)	0.045 (2)	0.066 (3)	−0.0032 (18)	0.0157 (19)	0.001 (2)
C111	0.043 (2)	0.036 (2)	0.046 (2)	−0.0047 (17)	0.0021 (18)	0.0016 (18)
C112	0.099 (4)	0.068 (3)	0.109 (4)	−0.040 (3)	0.066 (3)	−0.037 (3)
C113	0.125 (5)	0.061 (3)	0.084 (3)	0.022 (3)	0.052 (3)	0.026 (3)
C114	0.051 (2)	0.041 (2)	0.047 (2)	−0.0028 (18)	0.0087 (18)	−0.0046 (19)
C115	0.049 (2)	0.043 (2)	0.045 (2)	−0.009 (2)	0.0111 (18)	0.0103 (18)
C118	0.037 (2)	0.035 (2)	0.062 (3)	−0.0033 (18)	0.017 (2)	0.006 (2)
C121	0.055 (2)	0.040 (2)	0.100 (3)	−0.012 (2)	0.032 (2)	0.007 (2)

Table *S3. Geometric parameters (Å, °)*

O2—C1	1.442 (4)	C12—H123	1.000
O2—C3	1.431 (4)	C13—H131	1.000
O4—C3	1.433 (4)	C13—H132	1.000
O4—C5	1.422 (4)	C13—H133	1.000
O17—C7	1.442 (4)	C14—H141	1.000
O17—C18	1.355 (4)	C14—H142	1.000
O19—C18	1.190 (4)	C14—H143	1.000
O20—C18	1.319 (4)	C21—H211	1.000
O20—C21	1.460 (4)	C21—H212	1.000
O102—C101	1.418 (5)	C21—H213	1.000
O102—C103	1.424 (5)	C101—C105	1.543 (5)
O104—C103	1.425 (5)	C101—C109	1.525 (5)
O104—C105	1.425 (4)	C101—H1011	1.000
O117—C107	1.450 (4)	C103—C112	1.509 (6)
O117—C118	1.352 (4)	C103—C113	1.506 (6)
O119—C118	1.196 (4)	C105—C106	1.535 (5)
O120—C118	1.313 (4)	C105—H1051	1.000
O120—C121	1.452 (5)	C106—C107	1.569 (5)
N16—C15	1.143 (4)	C106—C111	1.509 (5)
N116—C115	1.142 (5)	C106—C114	1.531 (5)
C1—C5	1.540 (5)	C107—C108	1.541 (5)
C1—C9	1.521 (5)	C107—C115	1.483 (5)
C1—H11	1.000	C108—C109	1.540 (6)
C3—C12	1.503 (5)	C108—H1081	1.000
C3—C13	1.516 (5)	C108—H1082	1.000
C5—C6	1.556 (5)	C109—C110	1.495 (5)
C5—H51	1.000	C109—H1091	1.000
C6—C7	1.562 (5)	C110—C111	1.323 (5)
C6—C11	1.505 (5)	C110—H1101	1.000
C6—C14	1.519 (5)	C111—H1111	1.000
C7—C8	1.544 (5)	C112—H1121	1.000
C7—C15	1.490 (5)	C112—H1122	1.000
C8—C9	1.550 (5)	C112—H1123	1.000
C8—H81	1.000	C113—H1131	1.000
C8—H82	1.000	C113—H1132	1.000
C9—C10	1.489 (5)	C113—H1133	1.000
C9—H91	1.000	C114—H1141	1.000
C10—C11	1.315 (5)	C114—H1142	1.000
C10—H101	1.000	C114—H1143	1.000
C11—H111	1.000	C121—H1211	1.000
C12—H121	1.000	C121—H1212	1.000
C12—H122	1.000	C121—H1213	1.000
C1—O2—C3	106.9 (2)	C6—C5—H51	110.7
C3—O4—C5	107.3 (2)	C5—C6—C7	105.9 (3)
C7—O17—C18	118.6 (3)	C5—C6—C11	107.3 (3)
C18—O20—C21	115.1 (3)	C7—C6—C11	104.5 (3)
C101—O102—C103	108.4 (3)	C5—C6—C14	111.8 (3)
C103—O104—C105	108.1 (3)	C7—C6—C14	112.9 (3)
C107—O117—C118	117.3 (3)	C11—C6—C14	113.9 (3)
C118—O120—C121	114.8 (3)	C6—C7—O17	103.3 (3)
O2—C1—C5	104.2 (3)	C6—C7—C8	110.4 (3)
O2—C1—C9	110.8 (3)	O17—C7—C8	113.3 (3)
C5—C1—C9	109.7 (3)	C6—C7—C15	110.4 (3)
O2—C1—H11	110.6	O17—C7—C15	108.1 (3)
C5—C1—H11	110.7	C8—C7—C15	111.1 (3)
C9—C1—H11	110.6	C7—C8—C9	109.4 (3)
O4—C3—O2	104.4 (3)	C7—C8—H81	109.4
O4—C3—C12	111.2 (3)	C9—C8—H81	109.5
O2—C3—C12	110.9 (3)	C7—C8—H82	109.6
O4—C3—C13	107.5 (3)	C9—C8—H82	109.5
O2—C3—C13	108.7 (3)	H81—C8—H82	109.5
C12—C3—C13	113.7 (3)	C8—C9—C1	106.0 (3)
C1—C5—O4	105.0 (3)	C8—C9—C10	107.9 (3)
C1—C5—C6	110.8 (3)	C1—C9—C10	109.3 (3)
O4—C5—C6	108.9 (3)	C8—C9—H91	111.2
C1—C5—H51	110.6	C1—C9—H91	111.2
O4—C5—H51	110.6	C10—C9—H91	111.1

C9—C10—C11	114.3 (3)	C105—C106—C114	111.0 (3)
C9—C10—H101	122.8	C107—C106—C114	112.1 (3)
C11—C10—H101	122.9	C111—C106—C114	114.0 (3)
C6—C11—C10	116.8 (3)	C106—C107—O117	104.2 (3)
C6—C11—H111	121.6	C106—C107—C108	109.6 (3)
C10—C11—H111	121.5	O117—C107—C108	112.5 (3)
C3—C12—H121	109.6	C106—C107—C115	109.8 (3)
C3—C12—H122	109.6	O117—C107—C115	107.6 (3)
H121—C12—H122	109.5	C108—C107—C115	112.7 (3)
C3—C12—H123	109.2	C107—C108—C109	109.9 (3)
H121—C12—H123	109.5	C107—C108—H1081	109.4
H122—C12—H123	109.5	C109—C108—H1081	109.2
C3—C13—H131	109.5	C107—C108—H1082	109.3
C3—C13—H132	109.3	C109—C108—H1082	109.6
H131—C13—H132	109.5	H1081—C108—H1082	109.5
C3—C13—H133	109.6	C108—C109—C101	106.3 (3)
H131—C13—H133	109.5	C108—C109—C110	108.3 (3)
H132—C13—H133	109.5	C101—C109—C110	108.9 (3)
C6—C14—H141	109.4	C108—C109—H1091	111.1
C6—C14—H142	109.4	C101—C109—H1091	111.0
H141—C14—H142	109.5	C110—C109—H1091	111.1
C6—C14—H143	109.5	C109—C110—C111	115.0 (4)
H141—C14—H143	109.5	C109—C110—H1101	122.5
H142—C14—H143	109.5	C111—C110—H1101	122.5
C7—C15—N16	177.2 (4)	C106—C111—C110	115.1 (3)
O17—C18—O20	105.9 (3)	C106—C111—H1111	122.5
O17—C18—O19	125.4 (3)	C110—C111—H1111	122.4
O20—C18—O19	128.7 (3)	C103—C112—H1121	109.5
O20—C21—H211	109.5	C103—C112—H1122	109.7
O20—C21—H212	109.4	H1121—C112—H1122	109.5
H211—C21—H212	109.5	C103—C112—H1123	109.3
O20—C21—H213	109.5	H1121—C112—H1123	109.5
H211—C21—H213	109.5	H1122—C112—H1123	109.5
H212—C21—H213	109.5	C103—C113—H1131	109.5
O102—C101—C105	104.3 (3)	C103—C113—H1132	109.5
O102—C101—C109	111.6 (3)	H1131—C113—H1132	109.5
C105—C101—C109	108.5 (3)	C103—C113—H1133	109.3
O102—C101—H1011	110.8	H1131—C113—H1133	109.5
C105—C101—H1011	110.7	H1132—C113—H1133	109.5
C109—C101—H1011	110.7	C106—C114—H1141	109.5
O104—C103—O102	104.3 (3)	C106—C114—H1142	109.5
O104—C103—C112	110.5 (4)	H1141—C114—H1142	109.5
O102—C103—C112	110.4 (4)	C106—C114—H1143	109.5
O104—C103—C113	108.0 (4)	H1141—C114—H1143	109.5
O102—C103—C113	108.7 (4)	H1142—C114—H1143	109.5
C112—C103—C113	114.4 (4)	C107—C115—N116	176.2 (4)
C101—C105—O104	104.5 (3)	O117—C118—O120	106.4 (3)
C101—C105—C106	111.7 (3)	O117—C118—O119	125.9 (3)
O104—C105—C106	109.0 (3)	O120—C118—O119	127.6 (4)
C101—C105—H1051	110.5	O120—C121—H1211	109.5
O104—C105—H1051	110.4	O120—C121—H1212	109.4
C106—C105—H1051	110.5	H1211—C121—H1212	109.5
C105—C106—C107	106.2 (3)	O120—C121—H1213	109.5
C105—C106—C111	107.9 (3)	H1211—C121—H1213	109.5
C107—C106—C111	105.2 (3)	H1212—C121—H1213	109.5

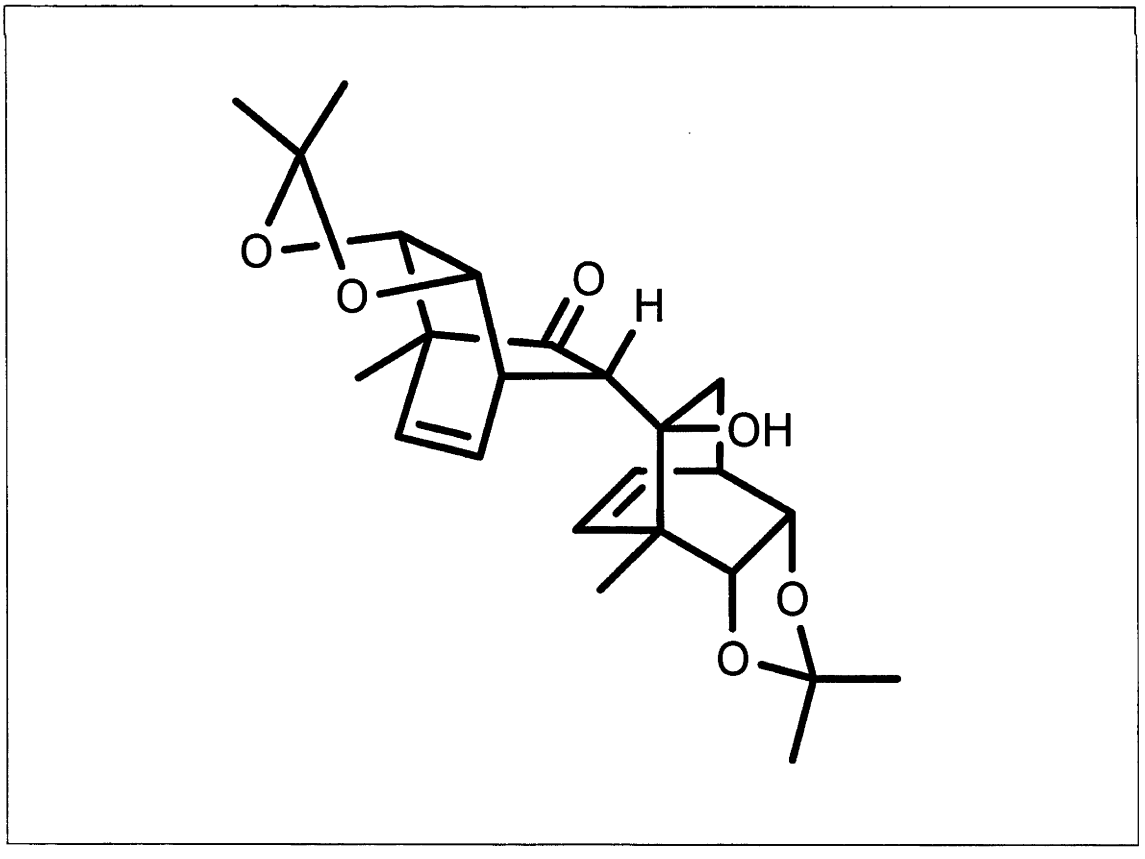
O2—C1—C5—O4	0.4 (3)	C5—C6—C7—C8	56.6 (3)
O2—C1—C5—C6	−117.1 (3)	C5—C6—C7—C15	−66.7 (4)
O2—C1—C9—C8	175.8 (2)	C5—C6—C11—C10	−54.9 (4)
O2—C1—C9—C10	59.7 (4)	C6—C5—C1—C9	1.6 (3)
O2—C3—O4—C5	−34.3 (3)	C6—C7—O17—C18	174.4 (3)
O4—C3—O2—C1	34.4 (3)	C6—C7—C8—C9	4.6 (4)
O4—C5—C1—C9	119.0 (3)	C6—C11—C10—C9	0.8 (5)
O4—C5—C6—C7	−175.8 (3)	C7—C6—C11—C10	57.2 (4)
O4—C5—C6—C11	−64.6 (4)	C7—C8—C9—C10	51.9 (4)
O4—C5—C6—C14	60.9 (4)	C8—C7—O17—C18	−66.1 (4)
O17—C7—C6—C5	178.0 (3)	C8—C7—C6—C11	−56.6 (3)
O17—C7—C6—C11	64.8 (3)	C8—C7—C6—C14	179.1 (3)
O17—C7—C6—C14	−59.5 (3)	C8—C9—C10—C11	−58.2 (5)
O17—C7—C8—C9	−110.7 (4)	C9—C8—C7—C15	127.4 (4)
O17—C18—O20—C21	177.2 (3)	C10—C11—C6—C14	−179.2 (4)
O19—C18—O17—C7	5.3 (6)	C11—C6—C7—C15	−179.9 (3)
O19—C18—O20—C21	−3.8 (6)	C14—C6—C7—C15	55.9 (4)
O20—C18—O17—C7	−175.6 (3)	C15—C7—O17—C18	57.4 (4)
O102—C101—C105—O104	0.6 (3)	C101—O102—C103—C112	−86.9 (4)
O102—C101—C105—C106	−117.1 (3)	C101—O102—C103—C113	146.8 (3)
O102—C101—C109—C108	175.5 (3)	C101—C105—O104—C103	18.7 (3)
O102—C101—C109—C110	58.9 (4)	C101—C105—C106—C107	−61.0 (3)
O102—C103—O104—C105	−31.2 (3)	C101—C105—C106—C111	51.3 (4)
O104—C103—O102—C101	31.8 (3)	C101—C105—C106—C114	176.9 (3)
O104—C105—C101—C109	119.7 (3)	C101—C109—C108—C107	−65.5 (4)
O104—C105—C106—C107	−176.0 (3)	C101—C109—C110—C111	57.5 (5)
O104—C105—C106—C111	−63.7 (4)	C103—O102—C101—C105	−19.9 (4)
O104—C105—C106—C114	61.9 (3)	C103—O102—C101—C109	−136.8 (3)
O117—C107—C106—C105	176.9 (3)	C103—O104—C105—C106	138.3 (3)
O117—C107—C106—C111	62.7 (3)	C105—O104—C103—C112	87.4 (4)
O117—C107—C106—C114	−61.7 (3)	C105—O104—C103—C113	−146.8 (4)
O117—C107—C108—C109	−110.5 (3)	C105—C101—C109—C108	61.1 (4)
O117—C118—O120—C121	−179.0 (3)	C105—C101—C109—C110	−55.4 (4)
O119—C118—O117—C107	−3.1 (6)	C105—C106—C107—C108	56.3 (3)
O119—C118—O120—C121	0.5 (6)	C105—C106—C107—C115	−68.0 (4)
O120—C118—O117—C107	176.3 (3)	C105—C106—C111—C110	−55.1 (5)
C1—O2—C3—C12	−85.5 (3)	C106—C105—C101—C109	2.0 (4)
C1—O2—C3—C13	148.7 (3)	C106—C107—O117—C118	179.8 (3)
C1—C5—O4—C3	20.6 (3)	C106—C107—C108—C109	5.0 (4)
C1—C5—C6—C7	−60.8 (3)	C106—C111—C110—C109	0.3 (5)
C1—C5—C6—C11	50.4 (3)	C107—C106—C111—C110	58.0 (4)
C1—C5—C6—C14	176.0 (3)	C107—C108—C109—C110	51.4 (4)
C1—C9—C8—C7	−65.1 (4)	C108—C107—O117—C118	−61.5 (4)
C1—C9—C10—C11	56.5 (4)	C108—C107—C106—C111	−58.0 (3)
C3—O2—C1—C5	−21.2 (3)	C108—C107—C106—C114	177.7 (3)
C3—O2—C1—C9	−139.2 (3)	C108—C109—C110—C111	−57.8 (5)
C3—O4—C5—C6	139.3 (3)	C109—C108—C107—C115	127.6 (4)
C5—O4—C3—C12	85.4 (3)	C110—C111—C106—C114	−178.8 (4)
C5—O4—C3—C13	−149.5 (3)	C111—C106—C107—C115	177.7 (3)
C5—C1—C9—C8	61.2 (3)	C114—C106—C107—C115	53.4 (4)
C5—C1—C9—C10	−54.8 (4)	C115—C107—O117—C118	63.3 (4)

Table *S4. Contact distances (Å)*

O2···C21^{i}	3.485 (5)	O119···C101^{vii}	3.468 (4)
O19···C21^{ii}	3.479 (5)	O120···C14	3.510 (4)
O19···C1^{iii}	3.501 (4)	N16···C21^{viii}	3.354 (5)
O20···C13^{iv}	3.509 (5)	N16···C9^{iii}	3.547 (5)
O20···C12^{v}	3.510 (4)	N116···C121^{vi}	3.247 (6)
O102···C121^{i}	3.207 (5)	N116···C101^{vii}	3.418 (5)
O102···O120^{i}	3.463 (4)	N116···C109^{vii}	3.427 (5)
O104···C14^{vi}	3.513 (5)	C10···C21^{i}	3.580 (5)

Symmetry codes: (i) $x, 1+y, z$; (ii) $1-x, y, -z$; (iii) $\frac{1}{2}-x, y-\frac{1}{2}, -z$; (iv) $x, y-1, z$; (v) $\frac{1}{2}+x, y-\frac{1}{2}, z$; (vi) $\frac{1}{2}+x, \frac{1}{2}+y, z$; (vii) $\frac{3}{2}-x, y-\frac{1}{2}, 1-z$; (viii) $x-\frac{1}{2}, \frac{1}{2}+y, z$.

A.5 X-ray crystal structure report for compound 153



Sample: ban0628

Compound: $C_{24}H_{32}O_6$

X-ray Structure Report

for

Christine Dietinger and Martin G. Banwell

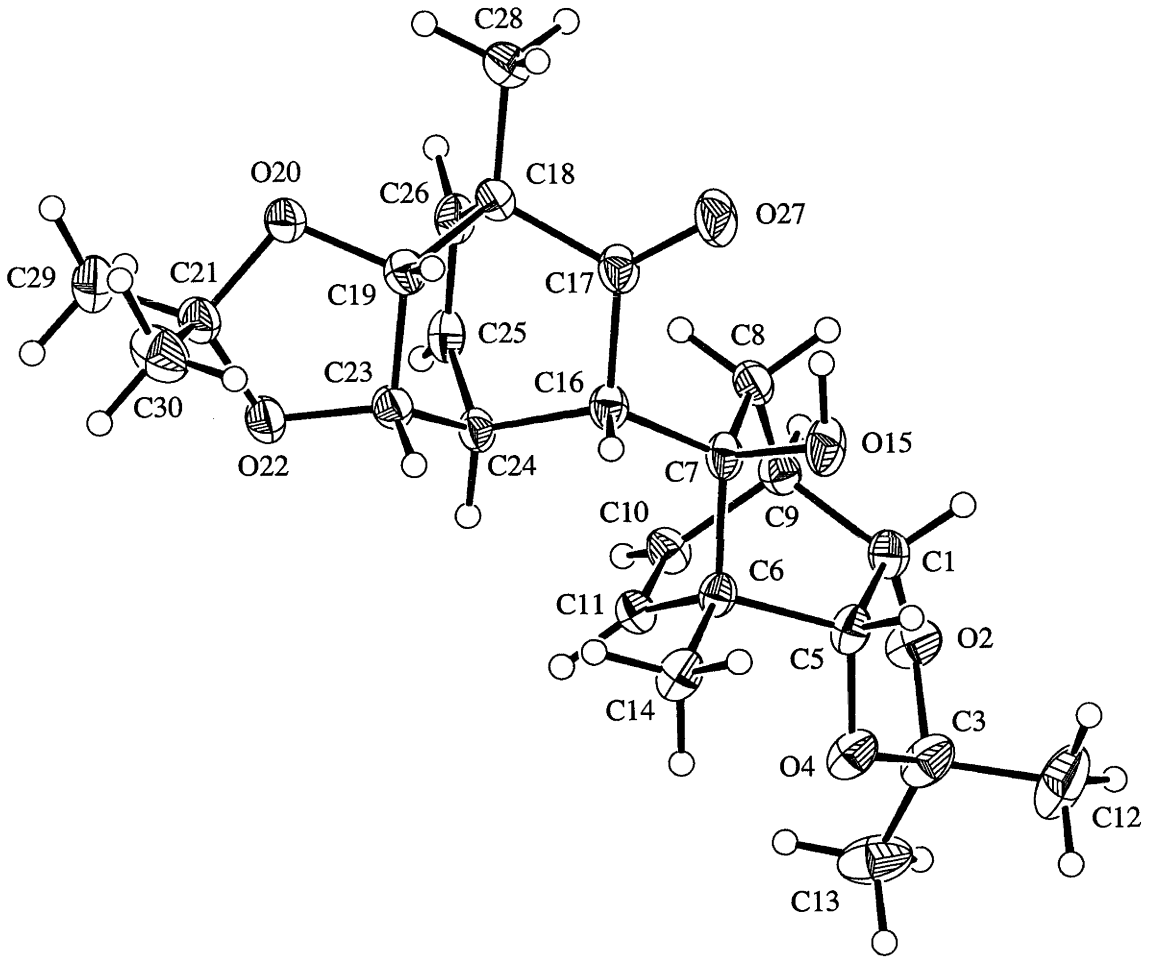
by

Anthony C. Willis

Research School of Chemistry, Institute of Advanced Studies

Australian National University, Canberra, ACT 0200, Australia

Friday, 22nd September, 2006


C28
O20
C26
C18
O27
C29
C21
C19
C17
C25
C8
C23
C16
C30
O15
O22
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C6
C11
O2
C5
C14
C3
O4
C12
C13

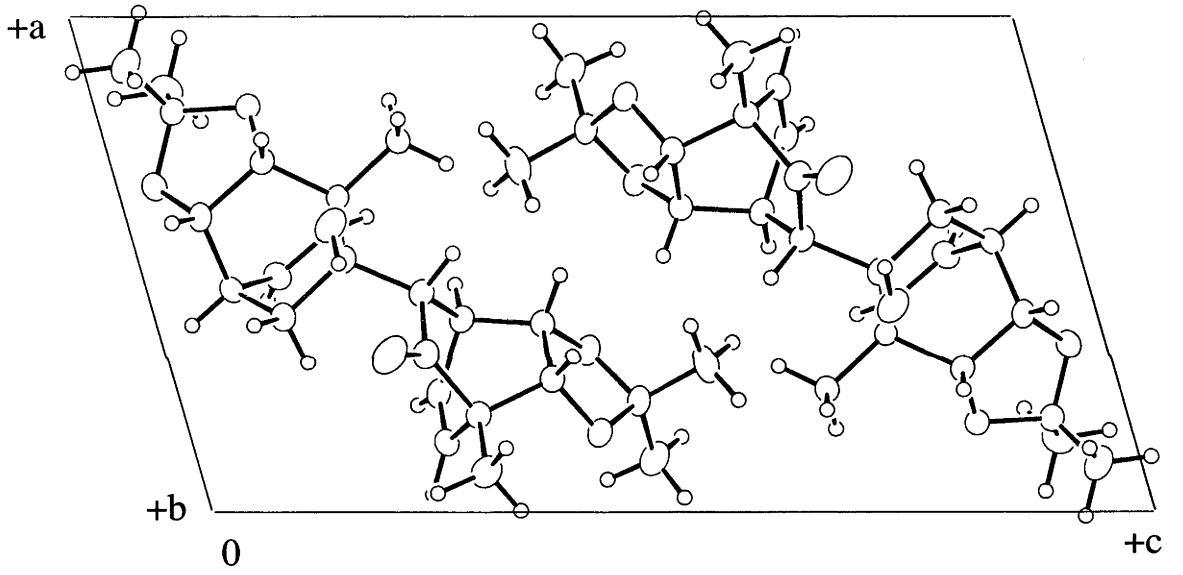
+a
+b
0
+c

Figure Captions for $C_{24}H_{32}O_6$

Figure 1. Molecular structure of $C_{24}H_{32}O_6$ with labelling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

Figure 2. Unit cell packing diagram of $C_{24}H_{32}O_6$ projected down the *b* axis. Hydrogen atoms are drawn as circles with small radii.

Assignment of Chiral Centres

C1	S	C5	R	C6	R	C7	R	C9	R
C16	S	C18	S	C19	R	C23	S	C24	S

Calculated by PLATON.
Spek, A.L. (2001). PLATON - A Multipurpose Crystallographic Tool, Utrecht University, Utrecht, The Netherlands.

22 Sep 2006

Crystal structure of $C_{24}H_{32}O_6$ –ban0628

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Abstract

The crystal structure of $C_{24}H_{32}O_6$ is reported.

Comment

The compound is enantiometrically pure but the anomolous dispersion terms are very low for all elements in the structure and so the absolute configuration can not be determined in this experiment. Consequently Friedel-pair reflections have been averaged and the Flack parameter has not been refined. The absolute configuration of the molecule has been assigned on the basis of the synthetic precursors.

The crystallographic asymmetric unit consists of one molecule of $C_{24}H_{32}O_6$.

The final difference electron density map is essentially featureless, with the largest peaks being located between atoms.

Experimental

The compound was prepared by CD and recrystallized from hexane. The sample ID is 2CD11*p*32–38recryst.

Crystal data

$C_{24}H_{32}O_6$

$M_r = 416.51$

Monoclinic

$P2_1$

$a = 9.4876\,(2)$ Å

$b = 7.0765\,(1)$ Å

$c = 17.2749\,(4)$ Å

$\beta = 105.6702\,(10)°$

$V = 1116.71\,(4)$ Å^3

$Z = 2$

$D_x = 1.239$ Mg m^{-3}

D_m not measured

Mo $K\alpha$ radiation

$\lambda = 0.71073$ Å

Cell parameters from 20551 reflections

$\theta = 3$–$27°$

$\mu = 0.088$ mm^{-1}

$T = 200$ K

Block

Colourless

$0.42 \times 0.24 \times 0.23$ mm

Crystal source: local

Data collection

Nonius KappaCCD diffractometer

φ and ω scans with CCD

Absorption correction:

by integration *via* Gaussian method (Coppens, 1970) implemented in maXus (2000)

$T_{min} = 0.973$, $T_{max} = 0.989$

25878 measured reflections

2769 independent reflections

2247 reflections with

$I > 3.0\sigma(I)$

$R_{int} = 0.039$

$\theta_{max} = 27.547°$

$h = -12 \rightarrow 12$

$k = -9 \rightarrow 9$

$l = -22 \rightarrow 22$

Refinement

Refinement on F

$R = 0.0283$

$wR = 0.0337$

$S = 1.1409$

2247 reflections

274 parameters

H atoms treated by a mixture of independent and constrained refinement

Method, part 1, Chebychev polynomial, (Carruthers & Watkin, 1979, Prince, 1982) [weight] = $1.0/[A_0{*}T_0(x) + A_1{*}T_1(x) \ldots + A_{n-1}]{*}T_{n-1}(x)]$ where A_i are the Chebychev coefficients listed below and x= Fcalc/Fmax Method = Robust Weighting (Prince, 1982) W = [weight] * [1-(deltaF/6*sigmaF)^2]^2 A_i are: 0.909 0.268 0.630

$(\Delta/\sigma)_{\max} = 0.001949$

$\Delta\rho_{\max} = 0.14$ e Å^{-3}

$\Delta\rho_{\min} = -0.13$ e Å^{-3}

Extinction correction: none

Scattering factors from International Tables Vol C 4.2.6.8 and 6.1.1.4

Absolute structure: The enantiomer has been assigned by reference to an unchanging chiral centre in the synthetic procedure.

Table 1. *Selected geometric parameters (Å, °)*

O2—C1	1.438 (2)	C7—C8	1.553 (2)
O2—C3	1.428 (2)	C7—C16	1.556 (2)
O4—C3	1.4217 (19)	C8—C9	1.539 (2)
O4—C5	1.429 (2)	C9—C10	1.499 (2)
O15—C7	1.4403 (17)	C10—C11	1.323 (2)
O20—C19	1.4226 (19)	C16—C17	1.531 (2)
O20—C21	1.429 (2)	C16—C24	1.550 (2)
O22—C21	1.4317 (19)	C17—C18	1.526 (2)
O22—C23	1.4271 (19)	C18—C19	1.547 (2)
O27—C17	1.215 (2)	C18—C26	1.513 (2)
C1—C5	1.541 (2)	C18—C28	1.521 (2)
C1—C9	1.528 (2)	C19—C23	1.542 (2)
C3—C12	1.520 (3)	C21—C29	1.500 (3)
C3—C13	1.507 (4)	C21—C30	1.520 (3)
C5—C6	1.5533 (19)	C23—C24	1.546 (2)
C6—C7	1.560 (2)	C24—C25	1.500 (2)
C6—C11	1.516 (2)	C25—C26	1.331 (3)
C6—C14	1.526 (2)		

C1—O2—C3	108.24 (13)	C9—C10—C11	114.43 (14)
C3—O4—C5	108.09 (13)	C6—C11—C10	115.86 (14)
C19—O20—C21	107.50 (12)	C7—C16—C17	111.87 (13)
C21—O22—C23	107.56 (13)	C7—C16—C24	120.53 (12)
O2—C1—C5	104.36 (13)	C17—C16—C24	107.11 (12)
O2—C1—C9	109.84 (14)	C16—C17—O27	123.09 (15)
C5—C1—C9	109.61 (12)	C16—C17—C18	114.19 (13)
O2—C3—O4	105.14 (13)	O27—C17—C18	122.71 (16)
O2—C3—C12	109.8 (2)	C17—C18—C19	106.14 (13)
O4—C3—C12	110.38 (19)	C17—C18—C26	103.09 (13)
O2—C3—C13	109.08 (18)	C19—C18—C26	107.35 (13)
O4—C3—C13	107.91 (19)	C17—C18—C28	112.64 (14)
C12—C3—C13	114.1 (2)	C19—C18—C28	111.76 (14)
C1—C5—O4	104.79 (12)	C26—C18—C28	115.11 (15)
C1—C5—C6	110.69 (12)	C18—C19—O20	108.28 (12)
O4—C5—C6	109.54 (13)	C18—C19—C23	111.24 (13)
C5—C6—C7	104.43 (12)	O20—C19—C23	104.84 (13)
C5—C6—C11	105.64 (12)	O22—C21—O20	104.93 (12)
C7—C6—C11	109.17 (11)	O22—C21—C29	108.64 (16)
C5—C6—C14	109.76 (12)	O20—C21—C29	108.63 (15)
C7—C6—C14	113.99 (13)	O22—C21—C30	111.24 (16)
C11—C6—C14	113.17 (13)	O20—C21—C30	109.42 (17)
C6—C7—O15	104.76 (13)	C29—C21—C30	113.59 (16)
C6—C7—C8	109.27 (12)	C19—C23—O22	104.69 (12)
O15—C7—C8	110.40 (13)	C19—C23—C24	109.85 (12)
C6—C7—C16	113.04 (12)	O22—C23—C24	111.08 (13)
O15—C7—C16	105.46 (12)	C23—C24—C16	103.80 (12)
C8—C7—C16	113.49 (13)	C23—C24—C25	107.92 (12)
C7—C8—C9	110.13 (13)	C16—C24—C25	109.81 (13)
C8—C9—C1	107.32 (13)	C24—C25—C26	115.23 (14)
C8—C9—C10	107.59 (12)	C18—C26—C25	115.74 (14)
C1—C9—C10	108.20 (13)		

Table 2. *Hydrogen-bonding geometry (Å, °)*

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O15—H1···O27	0.93 (3)	1.95 (3)	2.767 (2)	146 (2)

The alcohol H atom was located in a difference electron density map and refined positionally. Other H atoms were added at calculated positions and, during refinement, each rides on the C atom to which it is attached.

Data collection: *COLLECT* (Nonius BV, 1997). Cell refinement: Denzo/Scalepack (Otwinowski & Minor, 1997). Data reduction: Denzo/Scalepack . Program(s) used to solve structure: *SIR*92 (Altomare *et al.* 1994). Program(s) used to refine structure: *CRYSTALS* (Watkin *et al.*2003). Molecular graphics: *ORTEP*–II (Johnson 1976) in teXsan (MSC, 1992–1997) . Software used to prepare material for publication: *CRYSTALS* .

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Supplementary data

Table S1. *Fractional atomic coordinates and equivalent isotropic displacement parameters ($Å^2$)*

$$U_{eq} = (1/3)\Sigma_i\Sigma_j U^{ij} a^i a^j \mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	U_{eq}
O2	0.65937 (13)	0.2872 (2)	0.03947 (7)	0.0519
O4	0.82000 (12)	0.3186 (2)	0.16220 (7)	0.0473
O15	0.58144 (16)	0.74482 (18)	0.21399 (9)	0.0514
O20	0.16032 (13)	0.5466 (2)	0.43498 (7)	0.0450
O22	0.32825 (14)	0.31208 (19)	0.44849 (7)	0.0459
O27	0.31867 (19)	0.8675 (2)	0.23678 (10)	0.0664
C1	0.59811 (18)	0.4332 (3)	0.07840 (9)	0.0418
C3	0.8104 (2)	0.2666 (4)	0.08144 (10)	0.0548
C5	0.71013 (17)	0.4574 (3)	0.16097 (9)	0.0395
C6	0.63790 (16)	0.4174 (2)	0.22999 (8)	0.0333
C7	0.51174 (18)	0.5653 (2)	0.21716 (10)	0.0366
C8	0.39642 (18)	0.5245 (2)	0.13612 (9)	0.0401
C9	0.45182 (17)	0.3675 (2)	0.09007 (9)	0.0377
C10	0.47912 (18)	0.1952 (2)	0.14249 (10)	0.0397
C11	0.57253 (16)	0.2211 (2)	0.21386 (9)	0.0354
C12	0.9026 (3)	0.3985 (6)	0.04570 (15)	0.0884
C13	0.8525 (2)	0.0612 (4)	0.08100 (14)	0.0725
C14	0.75225 (18)	0.4340 (3)	0.31100 (9)	0.0460
C16	0.44502 (17)	0.5791 (2)	0.28992 (9)	0.0357
C17	0.32032 (18)	0.7233 (2)	0.27519 (10)	0.0415
C18	0.19624 (18)	0.6685 (2)	0.31157 (9)	0.0383
C19	0.26924 (17)	0.6213 (2)	0.40088 (9)	0.0385
C21	0.22464 (19)	0.3926 (3)	0.48584 (9)	0.0447
C23	0.38256 (17)	0.4613 (2)	0.40896 (9)	0.0378
C24	0.39183 (17)	0.3991 (2)	0.32471 (9)	0.0353
C25	0.24024 (19)	0.3490 (2)	0.27582 (9)	0.0400
C26	0.14079 (18)	0.4849 (3)	0.26943 (9)	0.0417
C28	0.0818 (2)	0.8233 (3)	0.30274 (13)	0.0559
C29	0.1081 (2)	0.2489 (3)	0.48496 (13)	0.0615
C30	0.2998 (3)	0.4670 (4)	0.56935 (11)	0.0666
H1	0.504 (3)	0.827 (4)	0.2111 (14)	0.0610
H11	0.58617 (18)	0.5535 (3)	0.04690 (9)	0.0508
H51	0.75333 (17)	0.5873 (3)	0.16635 (9)	0.0481
H81	0.37895 (18)	0.6421 (2)	0.10283 (9)	0.0483
H82	0.30276 (18)	0.4832 (2)	0.14697 (9)	0.0483
H91	0.37947 (17)	0.3408 (2)	0.03729 (9)	0.0441
H101	0.43068 (18)	0.0711 (2)	0.12495 (10)	0.0465
H111	0.59846 (16)	0.1176 (2)	0.25466 (9)	0.0421
H121	1.0082 (3)	0.3835 (6)	0.07533 (15)	0.1101
H122	0.8717 (3)	0.5322 (6)	0.05053 (15)	0.1101
H123	0.8885 (3)	0.3668 (6)	−0.01230 (15)	0.1101
H131	0.9582 (2)	0.0458 (4)	0.11032 (14)	0.0848
H132	0.8359 (2)	0.0173 (4)	0.02423 (14)	0.0848
H133	0.7913 (2)	−0.0155 (4)	0.10816 (14)	0.0848
H141	0.70525 (18)	0.4081 (3)	0.35522 (9)	0.0550
H142	0.79416 (18)	0.5646 (3)	0.31723 (9)	0.0550
H143	0.83224 (18)	0.3402 (3)	0.31362 (9)	0.0550
H161	0.52461 (17)	0.6324 (2)	0.33493 (9)	0.0438
H191	0.31535 (17)	0.7365 (2)	0.43077 (9)	0.0464
H231	0.48067 (17)	0.5040 (2)	0.44232 (9)	0.0454
H241	0.46138 (17)	0.2913 (2)	0.32793 (9)	0.0435
H251	0.21567 (19)	0.2225 (2)	0.24991 (9)	0.0494
H261	0.03610 (18)	0.4668 (3)	0.23870 (9)	0.0494
H281	0.0033 (2)	0.7806 (3)	0.32743 (13)	0.0692
H282	0.1290 (2)	0.9403 (3)	0.33057 (13)	0.0692
H283	0.0379 (2)	0.8509 (3)	0.24441 (13)	0.0692
H291	0.1517 (2)	0.1402 (3)	0.52036 (13)	0.0774

H292	0.0291 (2)	0.3080 (3)	0.50517 (13)	0.0774
H293	0.0658 (2)	0.2027 (3)	0.42876 (13)	0.0774
H301	0.3449 (3)	0.3593 (4)	0.60497 (11)	0.0783
H302	0.2262 (3)	0.5315 (4)	0.59216 (11)	0.0783
H303	0.3778 (3)	0.5591 (4)	0.56584 (11)	0.0783

Table *S2. Anisotropic displacement parameters* (Å^2)

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O2	0.0453 (6)	0.0737 (9)	0.0351 (5)	0.0028 (6)	0.0081 (5)	−0.0132 (6)
O4	0.0373 (5)	0.0706 (8)	0.0347 (5)	−0.0057 (6)	0.0110 (4)	−0.0124 (6)
O15	0.0683 (8)	0.0299 (6)	0.0662 (8)	−0.0152 (6)	0.0357 (7)	−0.0015 (5)
O20	0.0480 (6)	0.0521 (7)	0.0389 (6)	0.0106 (6)	0.0185 (5)	0.0112 (5)
O22	0.0567 (7)	0.0436 (6)	0.0435 (6)	0.0088 (6)	0.0239 (5)	0.0118 (5)
O27	0.0903 (11)	0.0346 (6)	0.0921 (11)	0.0103 (7)	0.0551 (9)	0.0211 (7)
C1	0.0485 (8)	0.0465 (9)	0.0321 (7)	−0.0040 (7)	0.0139 (6)	0.0005 (7)
C3	0.0423 (8)	0.0876 (15)	0.0358 (8)	−0.0042 (9)	0.0129 (6)	−0.0133 (9)
C5	0.0394 (7)	0.0455 (9)	0.0355 (7)	−0.0117 (7)	0.0133 (6)	−0.0040 (6)
C6	0.0337 (7)	0.0371 (7)	0.0299 (6)	−0.0075 (6)	0.0097 (5)	−0.0026 (6)
C7	0.0455 (8)	0.0266 (7)	0.0409 (7)	−0.0082 (6)	0.0174 (6)	0.0008 (6)
C8	0.0472 (8)	0.0373 (8)	0.0363 (7)	0.0034 (7)	0.0122 (6)	0.0082 (6)
C9	0.0394 (7)	0.0403 (8)	0.0307 (6)	−0.0031 (6)	0.0045 (5)	0.0009 (6)
C10	0.0438 (8)	0.0314 (7)	0.0410 (8)	−0.0064 (7)	0.0067 (6)	−0.0007 (6)
C11	0.0397 (7)	0.0310 (7)	0.0346 (7)	−0.0014 (6)	0.0086 (6)	0.0020 (6)
C12	0.0692 (13)	0.148 (3)	0.0579 (12)	−0.0276 (18)	0.0346 (11)	−0.0081 (17)
C13	0.0544 (11)	0.1003 (19)	0.0574 (11)	0.0215 (12)	0.0058 (9)	−0.0263 (12)
C14	0.0400 (8)	0.0643 (11)	0.0333 (7)	−0.0119 (8)	0.0093 (6)	−0.0095 (8)
C16	0.0426 (7)	0.0283 (7)	0.0385 (7)	−0.0057 (6)	0.0147 (6)	−0.0011 (6)
C17	0.0531 (9)	0.0291 (7)	0.0464 (8)	−0.0024 (7)	0.0204 (7)	0.0018 (7)
C18	0.0425 (8)	0.0361 (7)	0.0374 (7)	0.0041 (6)	0.0128 (6)	0.0078 (6)
C19	0.0431 (8)	0.0377 (8)	0.0352 (7)	−0.0004 (7)	0.0115 (6)	−0.0008 (6)
C21	0.0546 (9)	0.0493 (9)	0.0337 (7)	0.0105 (8)	0.0178 (7)	0.0086 (7)
C23	0.0410 (7)	0.0380 (8)	0.0345 (7)	0.0013 (6)	0.0106 (6)	0.0038 (6)
C24	0.0430 (8)	0.0280 (7)	0.0378 (7)	−0.0011 (6)	0.0159 (6)	0.0040 (6)
C25	0.0518 (8)	0.0355 (8)	0.0362 (7)	−0.0122 (7)	0.0177 (6)	−0.0015 (6)
C26	0.0417 (7)	0.0488 (9)	0.0332 (7)	−0.0100 (7)	0.0076 (6)	0.0032 (7)
C28	0.0600 (11)	0.0513 (10)	0.0617 (11)	0.0178 (9)	0.0257 (9)	0.0186 (9)
C29	0.0688 (11)	0.0638 (13)	0.0610 (11)	0.0011 (11)	0.0334 (9)	0.0161 (10)
C30	0.0882 (14)	0.0731 (14)	0.0346 (8)	0.0176 (13)	0.0099 (8)	0.0027 (9)

Table *S*3. *Geometric parameters (Å, °)*

O2—C1	1.438 (2)	C13—H131	1.000
O2—C3	1.428 (2)	C13—H132	1.000
O4—C3	1.4217 (19)	C13—H133	1.000
O4—C5	1.429 (2)	C14—H141	1.000
O15—C7	1.4403 (17)	C14—H142	1.000
O15—H1	0.93 (3)	C14—H143	1.000
O20—C19	1.4226 (19)	C16—C17	1.531 (2)
O20—C21	1.429 (2)	C16—C24	1.550 (2)
O22—C21	1.4317 (19)	C16—H161	1.000
O22—C23	1.4271 (19)	C17—C18	1.526 (2)
O27—C17	1.215 (2)	C18—C19	1.547 (2)
C1—C5	1.541 (2)	C18—C26	1.513 (2)
C1—C9	1.528 (2)	C18—C28	1.521 (2)
C1—H11	1.000	C19—C23	1.542 (2)
C3—C12	1.520 (3)	C19—H191	1.000
C3—C13	1.507 (4)	C21—C29	1.500 (3)
C5—C6	1.5533 (19)	C21—C30	1.520 (3)
C5—H51	1.000	C23—C24	1.546 (2)
C6—C7	1.560 (2)	C23—H231	1.000
C6—C11	1.516 (2)	C24—C25	1.500 (2)
C6—C14	1.526 (2)	C24—H241	1.000
C7—C8	1.553 (2)	C25—C26	1.331 (3)
C7—C16	1.556 (2)	C25—H251	1.000
C8—C9	1.539 (2)	C26—H261	1.000
C8—H81	1.000	C28—H281	1.000
C8—H82	1.000	C28—H282	1.000
C9—C10	1.499 (2)	C28—H283	1.000
C9—H91	1.000	C29—H291	1.000
C10—C11	1.323 (2)	C29—H292	1.000
C10—H101	1.000	C29—H293	1.000
C11—H111	1.000	C30—H301	1.000
C12—H121	1.000	C30—H302	1.000
C12—H122	1.000	C30—H303	1.000
C12—H123	1.000		

C1—O2—C3	108.24 (13)	H141—C14—H142	109.5
C3—O4—C5	108.09 (13)	C6—C14—H143	109.5
C7—O15—H1	100.9 (16)	H141—C14—H143	109.5
C19—O20—C21	107.50 (12)	H142—C14—H143	109.5
C21—O22—C23	107.56 (13)	C7—C16—C17	111.87 (13)
O2—C1—C5	104.36 (13)	C7—C16—C24	120.53 (12)
O2—C1—C9	109.84 (14)	C17—C16—C24	107.11 (12)
C5—C1—C9	109.61 (12)	C7—C16—H161	105.4
O2—C1—H11	110.9	C17—C16—H161	105.4
C5—C1—H11	110.9	C24—C16—H161	105.4
C9—C1—H11	110.9	C16—C17—O27	123.09 (15)
O2—C3—O4	105.14 (13)	C16—C17—C18	114.19 (13)
O2—C3—C12	109.8 (2)	O27—C17—C18	122.71 (16)
O4—C3—C12	110.38 (19)	C17—C18—C19	106.14 (13)
O2—C3—C13	109.08 (18)	C17—C18—C26	103.09 (13)
O4—C3—C13	107.91 (19)	C19—C18—C26	107.35 (13)
C12—C3—C13	114.1 (2)	C17—C18—C28	112.64 (14)
C1—C5—O4	104.79 (12)	C19—C18—C28	111.76 (14)
C1—C5—C6	110.69 (12)	C26—C18—C28	115.11 (15)
O4—C5—C6	109.54 (13)	C18—C19—O20	108.28 (12)
C1—C5—H51	110.6	C18—C19—C23	111.24 (13)
O4—C5—H51	110.6	O20—C19—C23	104.84 (13)
C6—C5—H51	110.6	C18—C19—H191	110.8
C5—C6—C7	104.43 (12)	O20—C19—H191	110.8
C5—C6—C11	105.64 (12)	C23—C19—H191	110.8
C7—C6—C11	109.17 (11)	O22—C21—O20	104.93 (12)
C5—C6—C14	109.76 (12)	O22—C21—C29	108.64 (16)
C7—C6—C14	113.99 (13)	O20—C21—C29	108.63 (15)
C11—C6—C14	113.17 (13)	O22—C21—C30	111.24 (16)
C6—C7—O15	104.76 (13)	O20—C21—C30	109.42 (17)
C6—C7—C8	109.27 (12)	C29—C21—C30	113.59 (16)
O15—C7—C8	110.40 (13)	C19—C23—O22	104.69 (12)
C6—C7—C16	113.04 (12)	C19—C23—C24	109.85 (12)
O15—C7—C16	105.46 (12)	O22—C23—C24	111.08 (13)
C8—C7—C16	113.49 (13)	C19—C23—H231	110.4
C7—C8—C9	110.13 (13)	O22—C23—H231	110.4
C7—C8—H81	109.3	C24—C23—H231	110.4
C9—C8—H81	109.3	C23—C24—C16	103.80 (12)
C7—C8—H82	109.3	C23—C24—C25	107.92 (12)
C9—C8—H82	109.3	C16—C24—C25	109.81 (13)
H81—C8—H82	109.5	C23—C24—H241	111.7
C8—C9—C1	107.32 (13)	C16—C24—H241	111.7
C8—C9—C10	107.59 (12)	C25—C24—H241	111.7
C1—C9—C10	108.20 (13)	C24—C25—C26	115.23 (14)
C8—C9—H91	111.2	C24—C25—H251	122.4
C1—C9—H91	111.2	C26—C25—H251	122.4
C10—C9—H91	111.2	C18—C26—C25	115.74 (14)
C9—C10—C11	114.43 (14)	C18—C26—H261	122.1
C9—C10—H101	122.8	C25—C26—H261	122.1
C11—C10—H101	122.8	C18—C28—H281	109.5
C6—C11—C10	115.86 (14)	C18—C28—H282	109.5
C6—C11—H111	122.1	H281—C28—H282	109.5
C10—C11—H111	122.1	C18—C28—H283	109.5
C3—C12—H121	109.5	H281—C28—H283	109.5
C3—C12—H122	109.5	H282—C28—H283	109.5
H121—C12—H122	109.5	C21—C29—H291	109.5
C3—C12—H123	109.4	C21—C29—H292	109.5
H121—C12—H123	109.5	H291—C29—H292	109.5
H122—C12—H123	109.5	C21—C29—H293	109.5
C3—C13—H131	109.5	H291—C29—H293	109.5
C3—C13—H132	109.5	H292—C29—H293	109.5
H131—C13—H132	109.5	C21—C30—H301	109.5
C3—C13—H133	109.5	C21—C30—H302	109.5
H131—C13—H133	109.5	H301—C30—H302	109.5
H132—C13—H133	109.5	C21—C30—H303	109.5
C6—C14—H141	109.5	H301—C30—H303	109.5
C6—C14—H142	109.5	H302—C30—H303	109.5

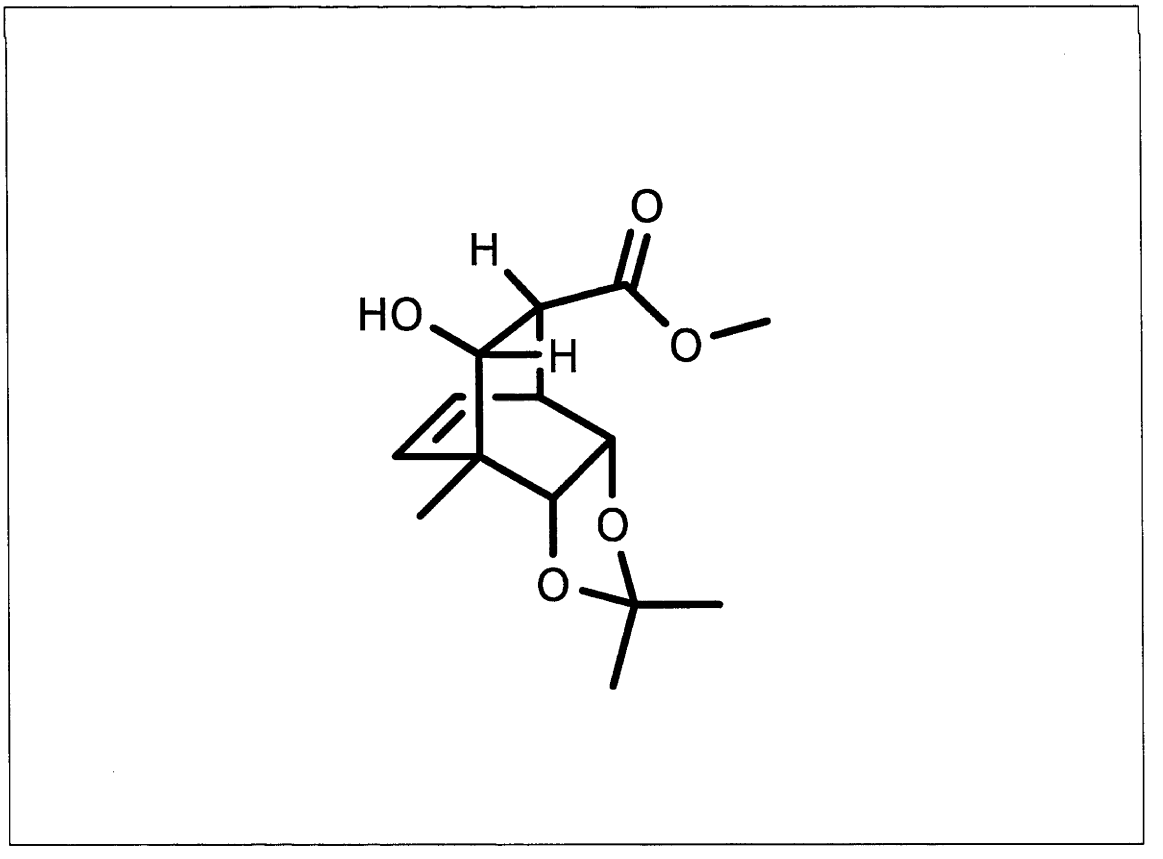
O2—C1—C5—O4	−2.3 (2)	C5—C6—C7—C16	−167.9 (1)
O2—C1—C5—C6	−120.4 (2)	C5—C6—C11—C10	−56.0 (2)
O2—C1—C9—C8	176.8 (1)	C6—C5—C1—C9	−2.8 (2)
O2—C1—C9—C10	61.0 (2)	C6—C7—C8—C9	−6.6 (2)
O2—C3—O4—C5	−30.9 (2)	C6—C7—C16—C17	−179.3 (1)
O4—C3—O2—C1	29.3 (2)	C6—C7—C16—C24	−52.0 (2)
O4—C5—C1—C9	115.2 (2)	C6—C11—C10—C9	−1.1 (2)
O4—C5—C6—C7	−174.9 (1)	C7—C6—C11—C10	55.8 (2)
O4—C5—C6—C11	−59.8 (1)	C7—C8—C9—C10	58.9 (2)
O4—C5—C6—C14	62.5 (2)	C7—C16—C17—C18	144.8 (1)
O15—C7—C6—C5	−53.6 (1)	C7—C16—C24—C23	162.2 (1)
O15—C7—C6—C11	−166.2 (1)	C7—C16—C24—C25	−82.6 (2)
O15—C7—C6—C14	66.2 (2)	C8—C7—C6—C11	−47.9 (2)
O15—C7—C8—C9	108.1 (2)	C8—C7—C6—C14	−175.5 (1)
O15—C7—C16—C17	66.9 (1)	C8—C7—C16—C17	−54.1 (2)
O15—C7—C16—C24	−165.9 (1)	C8—C7—C16—C24	73.1 (2)
O20—C19—C18—C17	−172.8 (1)	C8—C9—C10—C11	−57.2 (2)
O20—C19—C18—C26	−63.1 (2)	C9—C8—C7—C16	−133.8 (1)
O20—C19—C18—C28	64.1 (2)	C10—C11—C6—C14	−176.1 (2)
O20—C19—C23—O22	−1.1 (1)	C11—C6—C7—C16	79.5 (1)
O20—C19—C23—C24	118.2 (1)	C14—C6—C7—C16	−48.1 (2)
O20—C21—O22—C23	31.4 (1)	C16—C17—C18—C19	51.9 (2)
O22—C21—O20—C19	−32.2 (2)	C16—C17—C18—C26	−60.9 (2)
O22—C23—C19—C18	−118.0 (1)	C16—C17—C18—C28	174.5 (1)
O22—C23—C24—C16	177.4 (1)	C16—C24—C23—C19	62.1 (1)
O22—C23—C24—C25	60.9 (1)	C16—C24—C25—C26	−56.3 (2)
O27—C17—C16—C7	−34.1 (2)	C17—C16—C24—C23	−68.4 (1)
O27—C17—C16—C24	−168.2 (2)	C17—C16—C24—C25	46.7 (2)
O27—C17—C18—C19	−129.3 (2)	C17—C18—C19—C23	−58.1 (1)
O27—C17—C18—C26	118.0 (2)	C17—C18—C26—C25	56.1 (2)
O27—C17—C18—C28	−6.7 (2)	C18—C17—C16—C24	10.6 (2)
C1—O2—C3—C12	−89.5 (2)	C18—C19—O20—C21	139.2 (1)
C1—O2—C3—C13	144.8 (2)	C18—C19—C23—C24	1.4 (2)
C1—C5—O4—C3	20.3 (2)	C18—C26—C25—C24	0.6 (2)
C1—C5—C6—C7	−59.8 (2)	C19—O20—C21—C29	−148.2 (1)
C1—C5—C6—C11	55.3 (2)	C19—O20—C21—C30	87.3 (2)
C1—C5—C6—C14	177.6 (2)	C19—C18—C26—C25	−55.7 (2)
C1—C9—C8—C7	−57.3 (2)	C19—C23—O22—C21	−18.4 (1)
C1—C9—C10—C11	58.5 (2)	C19—C23—C24—C25	−54.4 (2)
C3—O2—C1—C5	−16.4 (2)	C21—O20—C19—C23	20.3 (1)
C3—O2—C1—C9	−133.8 (1)	C21—O22—C23—C24	−136.9 (1)
C3—O4—C5—C6	139.1 (1)	C23—O22—C21—C29	147.4 (1)
C5—O4—C3—C12	87.5 (2)	C23—O22—C21—C30	−86.8 (2)
C5—O4—C3—C13	−147.2 (2)	C23—C19—C18—C26	51.7 (2)
C5—C1—C9—C8	62.7 (2)	C23—C19—C18—C28	178.8 (1)
C5—C1—C9—C10	−53.1 (2)	C23—C24—C25—C26	56.2 (2)
C5—C6—C7—C8	64.7 (2)	C25—C26—C18—C28	179.2 (2)

Table *S4. Contact distances (Å)*

O2···C8^{i}	3.474 (2)	O20···C29^{iv}	3.514 (3)
O4···C26^{ii}	3.322 (2)	O27···C10^{iii}	3.419 (2)
O15···C11^{iii}	3.371 (2)	O27···C11^{iii}	3.569 (2)
O15···C10^{iii}	3.461 (2)	O27···C25^{iii}	3.590 (2)

Symmetry codes: (i) $1-x, y-\frac{1}{2}, -z$; (ii) $1+x, y, z$; (iii) $x, 1+y, z$; (iv) $-x, \frac{1}{2}+y, 1-z$.

A.6 X-ray crystal structure report for compound 154b



Sample: ban0709

Compound: $C_{14}H_{20}O_5$

X-ray Structure Report

for

Christine Dietinger and Martin G. Banwell

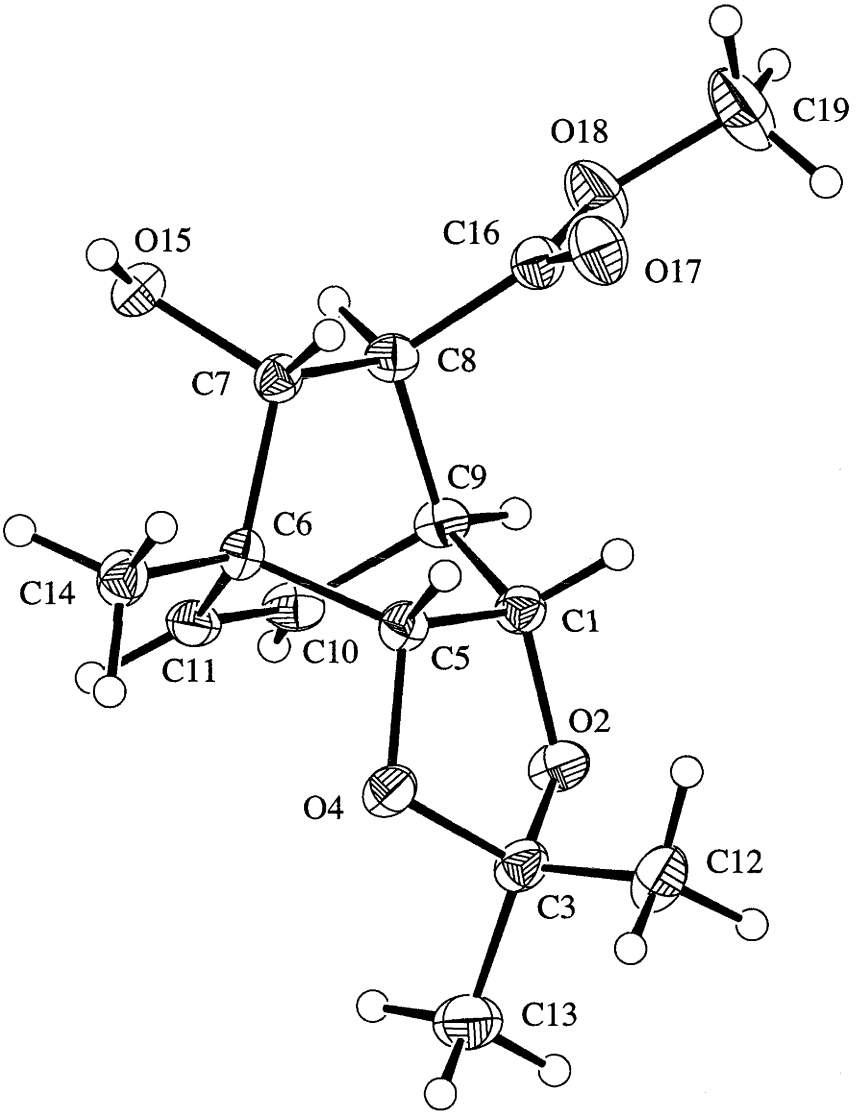
by

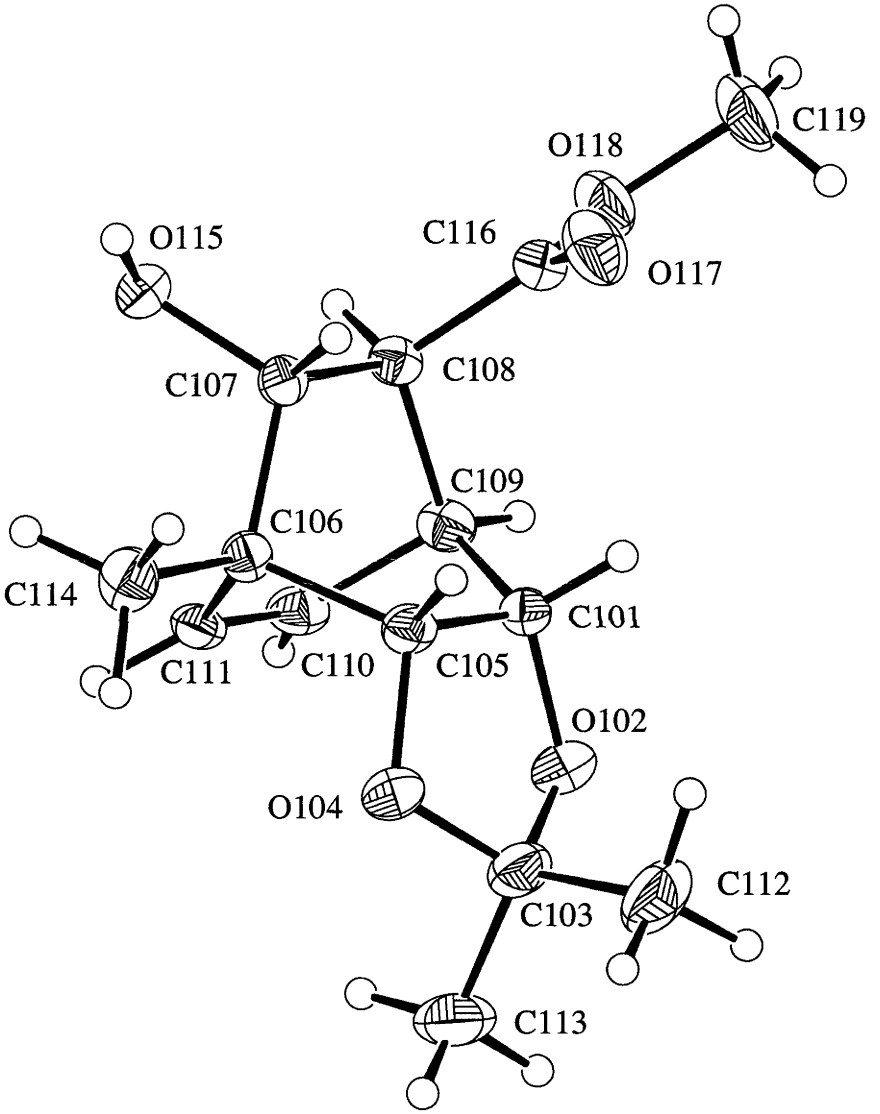
Anthony C. Willis

Research School of Chemistry,

The Australian National University, Canberra, ACT 0200, Australia

Wednesday, 31st January, 2007


C19
O18
C16
O17
O15
C8
C7
C9
C6
C14
C1
C11
C10
C5
O2
O4
C12
C3
C13


C119
O118
O115
C116
O117
C107
C108
C109
C106
C114
C101
C111
C110
C105
O102
O104
C112
C103
C113

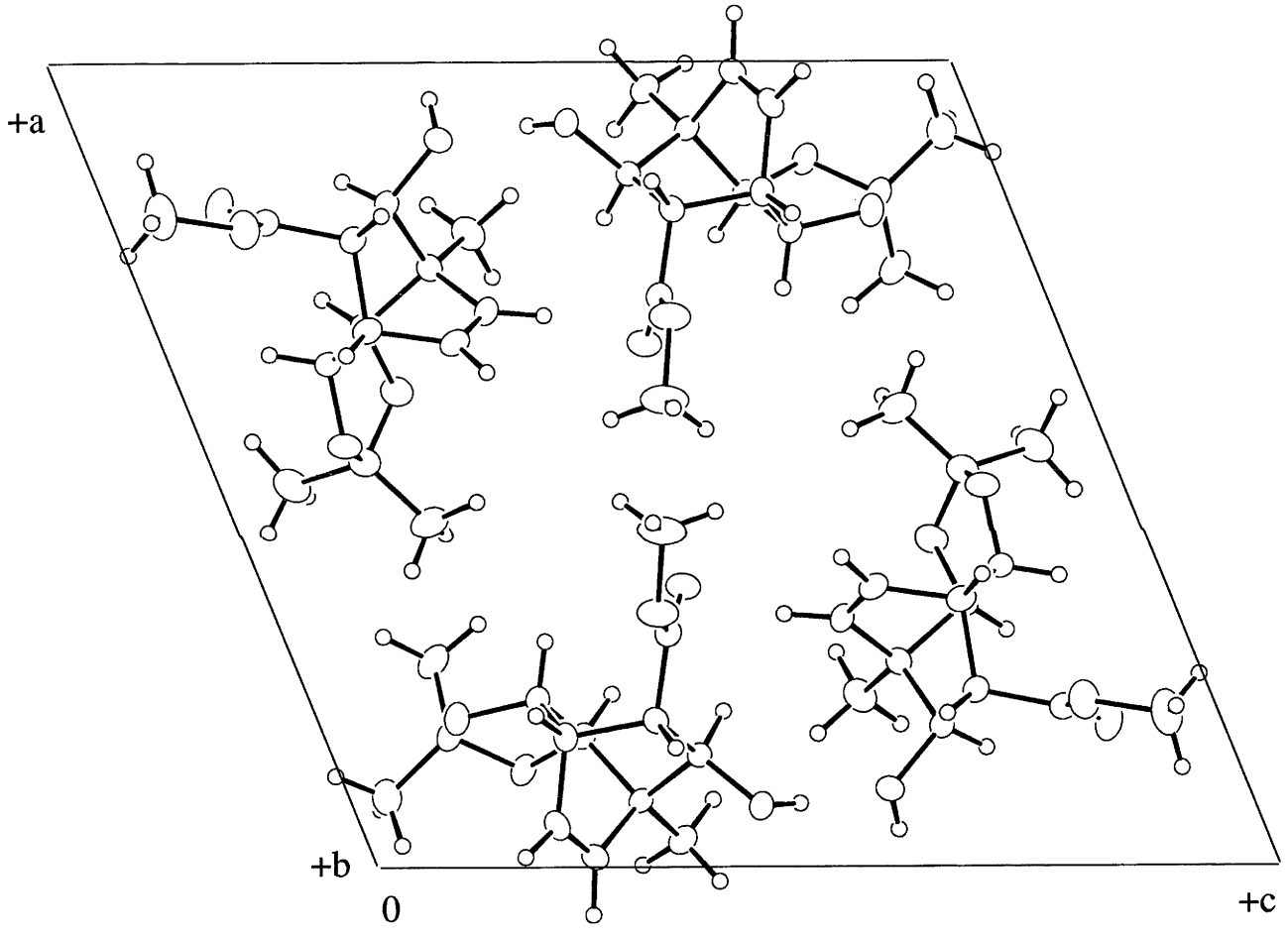

+a
+b
0
+c

Figure Captions for $C_{14}H_{20}O_5$

Figure 1. Structure of molecule one of $C_{14}H_{20}O_5$ with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

Figure 2. Structure of molecule two of $C_{14}H_{20}O_5$ with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

Figure 3. Unit cell packing diagram of $C_{14}H_{20}O_5$ projected down the *b* axis. Hydrogen atoms are drawn as circles with small radii.

Assignment of Chiral Centres

C1	S	C5	R	C6	R	C7	R	C8	S
C9	S								
C101	S	C105	R	C106	R	C107	R	C108	S
C109	S								

Calculated by PLATON.
Spek, A.L. (2001). PLATON - A Multipurpose Crystallographic Tool, Utrecht University, Utrecht, The Netherlands.

31 Jan 2007

Crystal structure of $C_{14}H_{20}O_5$ –ban0709

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Abstract

The crystal structure of $C_{14}H_{20}O_5$ is reported.

Comment

The compound is enantiometrically pure but the anomolous dispersion terms are very low for all elements in the structure and so the absolute configuration can not be determined in this experiment. Consequently Friedel-pair reflections have been averaged and the Flack parameter has not been refined. The absolute configuration of the molecule has been assigned on the basis of the synthetic precursors.

The crystallographic asymmetric unit consists of two molecules of $C_{14}H_{20}O_5$.

Crystals could only be obtained as very thin needles and they diffracted only weakly. Data were only collected to $2\theta = 25°$ as there were no measurable intensities beyond that point, even with long exposure times. The observation:parameter ratio is therefore lower than we would like, but the identity of the compound is clearly established and there do not appear to be any refinement anomalies.

The final difference electron density map is essentially featureless, with the largest peaks being located between atoms.

Experimental

The compound was prepared by CD and recrystallized from hexane/benzene. The sample ID is 3CD39*p*8–15.

Crystal data

$C_{14}H_{20}O_5$
$M_r = 268.31$
Monoclinic
$P2_1$
$a = 14.7414\,(4)$ Å
$b = 6.6985\,(2)$ Å
$c = 15.2998\,(5)$ Å
$\beta = 111.7498\,(19)°$
$V = 1403.23\,(8)$ Å^3
$Z = 4$
$D_x = 1.270$ Mg m^{-3}
D_m not measured
Mo $K\alpha$ radiation
$\lambda = 0.71073$ Å

Cell parameters from 10425 reflections
$\theta = 2.6–25°$
$\mu = 0.096$ mm^{-1}
$T = 200$ K
Needle
Colourless
0.42 × 0.05 × 0.04 mm
Crystal source: local

Data collection

Nonius KappaCCD diffractometer
φ and ω scans with CCD
Absorption correction:
by integration *via* Gaussian method (Coppens, 1970) implemented in maXus (2000)
$T_{min} = 0.976$, $T_{max} = 0.997$
15942 measured reflections
2697 independent reflections

2192 reflections with
$I > 1.5\sigma(I)$
$R_{int} = 0.048$
$\theta_{max} = 25.014°$
$h = -17 \rightarrow 17$
$k = -7 \rightarrow 7$
$l = -18 \rightarrow 18$

Refinement

Refinement on F
$R = 0.0307$
$wR = 0.0337$
$S = 1.1764$
2192 reflections
349 parameters
H atoms treated by a mixture of independent and constrained refinement

Method, part 1, Chebychev polynomial, (Carruthers & Watkin, 1979, Prince, 1982)
[weight] = $1.0/[A_0{*}T_0(x) + A_1{*}T_1(x) \ldots + A_{n-1}]{*}T_{n-1}(x)]$
where A_i are the Chebychev coefficients listed below and x= Fcalc/Fmax Method = Robust Weighting (Prince, 1982) W = [weight] * [1-(deltaF/6*sigmaF)^2]^2 A_i are: 0.894 0.569 0.694
$(\Delta/\sigma)_{max} = 0.000646$
$\Delta\rho_{max} = 0.11$ e Å^{-3}
$\Delta\rho_{min} = -0.15$ e Å^{-3}
Extinction correction: none
Scattering factors from International Tables Vol C 4.2.6.8 and 6.1.1.4

Table 1. *Selected geometric parameters (Å, °)*

O2—C1	1.430 (3)	C6—C7	1.550 (3)
O2—C3	1.435 (3)	C6—C11	1.507 (3)
O4—C3	1.429 (3)	C6—C14	1.515 (3)
O4—C5	1.429 (3)	C7—C8	1.540 (3)
O15—C7	1.437 (2)	C8—C9	1.562 (3)
O17—C16	1.204 (3)	C8—C16	1.513 (3)
O18—C16	1.338 (3)	C9—C10	1.507 (3)
O18—C19	1.449 (3)	C10—C11	1.324 (3)
O102—C101	1.428 (3)	C101—C105	1.533 (3)
O102—C103	1.421 (4)	C101—C109	1.530 (3)
O104—C103	1.420 (3)	C103—C112	1.515 (4)
O104—C105	1.429 (3)	C103—C113	1.510 (4)
O115—C107	1.435 (3)	C105—C106	1.548 (3)
O117—C116	1.197 (3)	C106—C107	1.546 (3)
O118—C116	1.340 (3)	C106—C111	1.512 (3)
O118—C119	1.451 (3)	C106—C114	1.515 (3)
C1—C5	1.537 (3)	C107—C108	1.536 (3)
C1—C9	1.531 (3)	C108—C109	1.562 (3)
C3—C12	1.505 (4)	C108—C116	1.512 (3)
C3—C13	1.502 (4)	C109—C110	1.503 (3)
C5—C6	1.548 (3)	C110—C111	1.320 (4)

C1—O2—C3	107.29 (17)	C8—C16—O18	110.45 (19)
C3—O4—C5	107.93 (15)	C8—C16—O17	126.3 (2)
C16—O18—C19	116.3 (2)	O18—C16—O17	123.3 (2)
C101—O102—C103	108.12 (19)	O102—C101—C105	104.94 (18)
C103—O104—C105	108.31 (19)	O102—C101—C109	109.86 (18)
C116—O118—C119	116.0 (3)	C105—C101—C109	110.00 (17)
O2—C1—C5	104.78 (17)	O102—C103—O104	105.97 (19)
O2—C1—C9	110.36 (17)	O102—C103—C112	110.7 (3)
C5—C1—C9	109.82 (16)	O104—C103—C112	110.3 (2)
O2—C3—O4	104.79 (17)	O102—C103—C113	108.3 (3)
O2—C3—C12	110.8 (2)	O104—C103—C113	107.3 (2)
O4—C3—C12	111.13 (19)	C112—C103—C113	113.9 (2)
O2—C3—C13	108.1 (2)	C101—C105—O104	104.90 (18)
O4—C3—C13	108.33 (19)	C101—C105—C106	110.81 (18)
C12—C3—C13	113.4 (2)	O104—C105—C106	109.82 (18)
C1—C5—O4	104.85 (16)	C105—C106—C107	104.25 (17)
C1—C5—C6	110.65 (17)	C105—C106—C111	106.91 (17)
O4—C5—C6	110.52 (16)	C107—C106—C111	108.40 (17)
C5—C6—C7	104.02 (16)	C105—C106—C114	111.32 (19)
C5—C6—C11	107.60 (17)	C107—C106—C114	111.66 (18)
C7—C6—C11	108.14 (17)	C111—C106—C114	113.8 (2)
C5—C6—C14	111.12 (17)	C106—C107—O115	111.75 (16)
C7—C6—C14	111.82 (17)	C106—C107—C108	110.21 (16)
C11—C6—C14	113.61 (18)	O115—C107—C108	108.99 (17)
C6—C7—O15	111.35 (15)	C107—C108—C109	110.00 (17)
C6—C7—C8	110.39 (16)	C107—C108—C116	112.71 (18)
O15—C7—C8	108.34 (17)	C109—C108—C116	109.88 (18)
C7—C8—C9	109.45 (16)	C101—C109—C108	106.76 (17)
C7—C8—C16	113.95 (17)	C101—C109—C110	107.97 (19)
C9—C8—C16	109.33 (17)	C108—C109—C110	106.70 (18)
C1—C9—C8	107.14 (17)	C109—C110—C111	114.8 (2)
C1—C9—C10	108.56 (18)	C106—C111—C110	115.77 (19)
C8—C9—C10	106.66 (17)	C108—C116—O118	110.6 (2)
C9—C10—C11	114.17 (19)	C108—C116—O117	126.2 (2)
C6—C11—C10	116.01 (18)	O118—C116—O117	123.2 (2)

Table 2. *Hydrogen-bonding geometry (Å, °)*

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O15—H1···O115	0.86 (3)	1.94 (3)	2.802 (2)	176 (2)
O115—H2···O15^{i}	0.86 (3)	2.00 (3)	2.839 (2)	169 (3)

Symmetry codes: (i) $-x, y-\frac{1}{2}, 1-z$.

The alcohol H atoms were located in a difference electron density map and refined positionally. Other H atoms were added at calculated positions and, during refinement, each rides on the C atom to which it is attached.

Data collection: *COLLECT* (Nonius BV, 1997). Cell refinement: Denzo/Scalepack (Otwinowski & Minor, 1997). Data reduction: Denzo/Scalepack (Otwinowski & Minor, 1997). Program(s) used to solve structure: *SIR*92 (Altomare *et al.* 1994). Program(s) used to refine structure: *CRYSTALS* (Watkin *et al.*2003). Molecular graphics: *ORTEP*–II (Johnson 1976) in teXsan (MSC, 1992–1997) . Software used to prepare material for publication: *CRYSTALS* (Watkin *et al.*2003).

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Supplementary data

Table S1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å²)*

$$U_{eq} = (1/3)\Sigma_i\Sigma_j U^{ij} a^i a^j \mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	U_{eq}
O2	0.18435 (12)	0.7444 (2)	0.15486 (10)	0.0386
O4	0.12088 (11)	0.4801 (2)	0.20550 (11)	0.0370
O15	0.07520 (10)	0.8847 (3)	0.45256 (11)	0.0355
O17	0.34824 (12)	0.8938 (3)	0.46541 (12)	0.0483
O18	0.31508 (13)	1.2145 (3)	0.42520 (15)	0.0537
O102	0.47427 (12)	0.5623 (3)	0.84359 (13)	0.0506
O104	0.40653 (12)	0.2832 (3)	0.76123 (12)	0.0482
O115	0.09563 (11)	0.6244 (2)	0.60207 (10)	0.0361
O117	0.17766 (15)	0.6591 (4)	0.87412 (14)	0.0622
O118	0.20512 (15)	0.9817 (3)	0.85670 (13)	0.0591
C1	0.20762 (16)	0.7808 (3)	0.25290 (15)	0.0323
C3	0.16345 (17)	0.5354 (3)	0.13895 (16)	0.0369
C5	0.16246 (15)	0.6042 (3)	0.28658 (15)	0.0308
C6	0.08245 (14)	0.6777 (3)	0.32185 (15)	0.0294
C7	0.13836 (14)	0.8134 (3)	0.40687 (14)	0.0294
C8	0.18170 (15)	0.9952 (3)	0.37445 (13)	0.0311
C9	0.16107 (16)	0.9764 (3)	0.26701 (14)	0.0316
C10	0.05192 (16)	0.9599 (3)	0.21785 (15)	0.0362
C11	0.01268 (15)	0.8065 (4)	0.24568 (14)	0.0350
C12	0.25547 (19)	0.4190 (4)	0.1546 (2)	0.0493
C13	0.0876 (2)	0.5105 (5)	0.04179 (18)	0.0537
C14	0.03352 (17)	0.5039 (4)	0.35020 (16)	0.0387
C16	0.29016 (17)	1.0231 (4)	0.42766 (15)	0.0357
C19	0.4182 (2)	1.2605 (5)	0.4686 (3)	0.0732
C101	0.37227 (15)	0.5794 (4)	0.82530 (15)	0.0373
C103	0.49429 (18)	0.3603 (5)	0.82880 (18)	0.0508
C105	0.32630 (16)	0.3920 (4)	0.76864 (16)	0.0358
C106	0.25361 (15)	0.4486 (3)	0.66927 (15)	0.0324
C107	0.17403 (15)	0.5722 (3)	0.68792 (14)	0.0323
C108	0.21844 (15)	0.7641 (3)	0.74177 (15)	0.0334
C109	0.33116 (16)	0.7664 (3)	0.76652 (16)	0.0375
C110	0.34654 (16)	0.7460 (4)	0.67518 (17)	0.0396
C111	0.30759 (16)	0.5845 (4)	0.62621 (15)	0.0378
C112	0.5229 (2)	0.2424 (6)	0.9195 (2)	0.0732
C113	0.5704 (2)	0.3578 (6)	0.7845 (2)	0.0714
C114	0.2112 (2)	0.2644 (4)	0.61097 (18)	0.0486
C116	0.19685 (16)	0.7896 (4)	0.83035 (16)	0.0410
C119	0.1887 (3)	1.0251 (6)	0.9426 (2)	0.0854
H1	0.0785 (18)	0.802 (5)	0.4966 (19)	0.0430
H2	0.046 (2)	0.550 (4)	0.5938 (18)	0.0430
H11	0.27999 (16)	0.7844 (3)	0.28737 (15)	0.0397
H51	0.21423 (15)	0.5297 (3)	0.33766 (15)	0.0380
H71	0.19276 (14)	0.7350 (3)	0.45317 (14)	0.0355
H81	0.14758 (15)	1.1174 (3)	0.38409 (13)	0.0367
H91	0.18756 (16)	1.0935 (3)	0.24353 (14)	0.0385
H101	0.01252 (16)	1.0563 (3)	0.16849 (15)	0.0414
H111	−0.05895 (15)	0.7779 (4)	0.21783 (14)	0.0405
H121	0.23931 (19)	0.2739 (4)	0.1432 (2)	0.0651
H122	0.30201 (19)	0.4384 (4)	0.2209 (2)	0.0651
H123	0.28621 (19)	0.4672 (4)	0.1102 (2)	0.0651
H131	0.0719 (2)	0.3656 (5)	0.02915 (18)	0.0650
H132	0.1134 (2)	0.5644 (5)	−0.00547 (18)	0.0650
H133	0.0272 (2)	0.5850 (5)	0.03700 (18)	0.0650
H141	−0.01772 (17)	0.5554 (4)	0.37265 (16)	0.0490
H142	0.08340 (17)	0.4271 (4)	0.40191 (16)	0.0490
H143	0.00260 (17)	0.4144 (4)	0.29475 (16)	0.0490
H191	0.4283 (2)	1.4067 (5)	0.4627 (3)	0.0829

H192	0.4425 (2)	1.2228 (5)	0.5367 (3)	0.0829
H193	0.4550 (2)	1.1836 (5)	0.4364 (3)	0.0829
H1011	0.36042 (15)	0.5835 (4)	0.88553 (15)	0.0450
H1051	0.29277 (16)	0.3113 (4)	0.80271 (16)	0.0429
H1071	0.14693 (15)	0.4907 (3)	0.72735 (14)	0.0393
H1081	0.18950 (15)	0.8802 (3)	0.69957 (15)	0.0410
H1091	0.36189 (16)	0.8909 (3)	0.80088 (16)	0.0458
H1101	0.38341 (16)	0.8468 (4)	0.65322 (17)	0.0496
H1111	0.31342 (16)	0.5541 (4)	0.56452 (15)	0.0476
H1121	0.5367 (2)	0.1009 (6)	0.9076 (2)	0.0827
H1122	0.5827 (2)	0.3027 (6)	0.9676 (2)	0.0827
H1123	0.4683 (2)	0.2458 (6)	0.9433 (2)	0.0827
H1131	0.5854 (2)	0.2166 (6)	0.7736 (2)	0.0890
H1132	0.6312 (2)	0.4246 (6)	0.8276 (2)	0.0890
H1133	0.5449 (2)	0.4306 (6)	0.7231 (2)	0.0890
H1141	0.1647 (2)	0.3055 (4)	0.54733 (18)	0.0554
H1142	0.1759 (2)	0.1827 (4)	0.64298 (18)	0.0554
H1143	0.2652 (2)	0.1833 (4)	0.60414 (18)	0.0554
H1191	0.1966 (3)	1.1716 (6)	0.9557 (2)	0.1031
H1192	0.2371 (3)	0.9501 (6)	0.9961 (2)	0.1031
H1193	0.1210 (3)	0.9835 (6)	0.9350 (2)	0.1031

Table *S2. Anisotropic displacement parameters* (Å^2)

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O2	0.0547 (9)	0.0307 (8)	0.0354 (8)	−0.0063 (7)	0.0226 (7)	−0.0024 (7)
O4	0.0491 (9)	0.0297 (8)	0.0413 (8)	−0.0084 (7)	0.0272 (7)	−0.0064 (7)
O15	0.0401 (8)	0.0375 (8)	0.0326 (8)	0.0064 (7)	0.0178 (6)	0.0018 (7)
O17	0.0349 (8)	0.0500 (10)	0.0543 (10)	0.0031 (8)	0.0100 (8)	0.0084 (9)
O18	0.0391 (9)	0.0364 (9)	0.0779 (12)	−0.0086 (7)	0.0128 (8)	−0.0043 (9)
O102	0.0306 (8)	0.0625 (12)	0.0540 (10)	0.0038 (8)	0.0102 (7)	0.0000 (9)
O104	0.0432 (9)	0.0484 (10)	0.0489 (9)	0.0179 (8)	0.0120 (7)	0.0057 (8)
O115	0.0311 (8)	0.0375 (9)	0.0368 (8)	−0.0016 (7)	0.0092 (6)	0.0057 (7)
O117	0.0753 (13)	0.0744 (15)	0.0495 (11)	−0.0083 (11)	0.0378 (11)	−0.0008 (10)
O118	0.0753 (13)	0.0558 (12)	0.0478 (10)	0.0145 (10)	0.0247 (9)	−0.0142 (9)
C1	0.0371 (10)	0.0312 (11)	0.0310 (10)	−0.0033 (9)	0.0155 (9)	−0.0010 (9)
C3	0.0468 (12)	0.0319 (11)	0.0394 (12)	−0.0068 (10)	0.0246 (10)	−0.0043 (10)
C5	0.0343 (11)	0.0256 (10)	0.0351 (11)	0.0014 (9)	0.0158 (9)	−0.0001 (9)
C6	0.0290 (10)	0.0301 (11)	0.0324 (11)	0.0003 (9)	0.0150 (9)	0.0017 (9)
C7	0.0294 (9)	0.0298 (10)	0.0296 (10)	0.0040 (9)	0.0117 (8)	0.0007 (9)
C8	0.0346 (11)	0.0267 (11)	0.0306 (11)	0.0020 (9)	0.0104 (9)	−0.0008 (9)
C9	0.0418 (12)	0.0249 (10)	0.0294 (10)	−0.0018 (9)	0.0148 (9)	0.0021 (9)
C10	0.0432 (12)	0.0319 (11)	0.0285 (10)	0.0051 (10)	0.0073 (9)	0.0021 (9)
C11	0.0318 (10)	0.0375 (12)	0.0318 (11)	0.0042 (9)	0.0073 (9)	−0.0059 (10)
C12	0.0580 (15)	0.0422 (15)	0.0626 (16)	−0.0001 (11)	0.0399 (13)	−0.0027 (12)
C13	0.0642 (16)	0.0543 (17)	0.0440 (13)	−0.0118 (13)	0.0218 (12)	−0.0108 (13)
C14	0.0411 (12)	0.0346 (12)	0.0467 (12)	−0.0052 (10)	0.0238 (10)	−0.0039 (10)
C16	0.0373 (12)	0.0352 (12)	0.0360 (11)	−0.0023 (10)	0.0152 (9)	−0.0012 (10)
C19	0.0406 (14)	0.062 (2)	0.105 (2)	−0.0187 (14)	0.0126 (15)	−0.0120 (18)
C101	0.0291 (10)	0.0494 (14)	0.0338 (11)	0.0014 (10)	0.0123 (9)	0.0000 (10)
C103	0.0397 (13)	0.0620 (18)	0.0478 (14)	0.0143 (12)	0.0129 (11)	0.0145 (13)
C105	0.0368 (11)	0.0334 (11)	0.0372 (12)	0.0068 (10)	0.0138 (10)	0.0078 (10)
C106	0.0360 (11)	0.0284 (11)	0.0318 (11)	0.0036 (9)	0.0114 (9)	0.0032 (9)
C107	0.0327 (10)	0.0344 (11)	0.0310 (10)	0.0006 (9)	0.0134 (8)	0.0048 (9)
C108	0.0345 (11)	0.0315 (11)	0.0366 (11)	0.0023 (9)	0.0159 (9)	0.0016 (9)
C109	0.0338 (11)	0.0350 (13)	0.0458 (12)	−0.0054 (10)	0.0173 (10)	−0.0059 (10)
C110	0.0348 (11)	0.0407 (14)	0.0484 (13)	0.0036 (10)	0.0214 (10)	0.0089 (11)
C111	0.0401 (11)	0.0444 (14)	0.0345 (11)	0.0151 (10)	0.0203 (10)	0.0109 (10)
C112	0.0557 (16)	0.096 (3)	0.0555 (17)	0.0125 (18)	0.0059 (14)	0.0308 (18)
C113	0.0484 (15)	0.095 (3)	0.079 (2)	0.0258 (17)	0.0332 (14)	0.0198 (19)
C114	0.0558 (14)	0.0353 (14)	0.0475 (13)	0.0030 (11)	0.0106 (11)	−0.0064 (11)
C116	0.0343 (11)	0.0519 (15)	0.0374 (12)	0.0043 (11)	0.0140 (10)	−0.0049 (12)
C119	0.109 (3)	0.098 (3)	0.0509 (17)	0.034 (2)	0.0316 (18)	−0.0206 (19)

Table S3. *Geometric parameters (Å, °)*

O2—C1	1.430 (3)	C13—H131	1.000
O2—C3	1.435 (3)	C13—H132	1.000
O4—C3	1.429 (3)	C13—H133	1.000
O4—C5	1.429 (3)	C14—H141	1.000
O15—C7	1.437 (2)	C14—H142	1.000
O15—H1	0.86 (3)	C14—H143	1.000
O17—C16	1.204 (3)	C19—H191	1.000
O18—C16	1.338 (3)	C19—H192	1.000
O18—C19	1.449 (3)	C19—H193	1.000
O102—C101	1.428 (3)	C101—C105	1.533 (3)
O102—C103	1.421 (4)	C101—C109	1.530 (3)
O104—C103	1.420 (3)	C101—H1011	1.000
O104—C105	1.429 (3)	C103—C112	1.515 (4)
O115—C107	1.435 (3)	C103—C113	1.510 (4)
O115—H2	0.86 (3)	C105—C106	1.548 (3)
O117—C116	1.197 (3)	C105—H1051	1.000
O118—C116	1.340 (3)	C106—C107	1.546 (3)
O118—C119	1.451 (3)	C106—C111	1.512 (3)
C1—C5	1.537 (3)	C106—C114	1.515 (3)
C1—C9	1.531 (3)	C107—C108	1.536 (3)
C1—H11	1.000	C107—H1071	1.000
C3—C12	1.505 (4)	C108—C109	1.562 (3)
C3—C13	1.502 (4)	C108—C116	1.512 (3)
C5—C6	1.548 (3)	C108—H1081	1.000
C5—H51	1.000	C109—C110	1.503 (3)
C6—C7	1.550 (3)	C109—H1091	1.000
C6—C11	1.507 (3)	C110—C111	1.320 (4)
C6—C14	1.515 (3)	C110—H1101	1.000
C7—C8	1.540 (3)	C111—H1111	1.000
C7—H71	1.000	C112—H1121	1.000
C8—C9	1.562 (3)	C112—H1122	1.000
C8—C16	1.513 (3)	C112—H1123	1.000
C8—H81	1.000	C113—H1131	1.000
C9—C10	1.507 (3)	C113—H1132	1.000
C9—H91	1.000	C113—H1133	1.000
C10—C11	1.324 (3)	C114—H1141	1.000
C10—H101	1.000	C114—H1142	1.000
C11—H111	1.000	C114—H1143	1.000
C12—H121	1.000	C119—H1191	1.000
C12—H122	1.000	C119—H1192	1.000
C12—H123	1.000	C119—H1193	1.000
C1—O2—C3	107.29 (17)	C5—C6—C7	104.02 (16)
C3—O4—C5	107.93 (15)	C5—C6—C11	107.60 (17)
C7—O15—H1	107.9 (18)	C7—C6—C11	108.14 (17)
C16—O18—C19	116.3 (2)	C5—C6—C14	111.12 (17)
C101—O102—C103	108.12 (19)	C7—C6—C14	111.82 (17)
C103—O104—C105	108.31 (19)	C11—C6—C14	113.61 (18)
C107—O115—H2	110.5 (18)	C6—C7—O15	111.35 (15)
C116—O118—C119	116.0 (3)	C6—C7—C8	110.39 (16)
O2—C1—C5	104.78 (17)	O15—C7—C8	108.34 (17)
O2—C1—C9	110.36 (17)	C6—C7—H71	108.9
C5—C1—C9	109.82 (16)	O15—C7—H71	108.9
O2—C1—H11	110.6	C8—C7—H71	108.9
C5—C1—H11	110.6	C7—C8—C9	109.45 (16)
C9—C1—H11	110.6	C7—C8—C16	113.95 (17)
O2—C3—O4	104.79 (17)	C9—C8—C16	109.33 (17)
O2—C3—C12	110.8 (2)	C7—C8—H81	108.0
O4—C3—C12	111.13 (19)	C9—C8—H81	108.0
O2—C3—C13	108.1 (2)	C16—C8—H81	108.0
O4—C3—C13	108.33 (19)	C1—C9—C8	107.14 (17)
C12—C3—C13	113.4 (2)	C1—C9—C10	108.56 (18)
C1—C5—O4	104.85 (16)	C8—C9—C10	106.66 (17)
C1—C5—C6	110.65 (17)	C1—C9—H91	111.4
O4—C5—C6	110.52 (16)	C8—C9—H91	111.4
C1—C5—H51	110.2	C10—C9—H91	111.4
O4—C5—H51	110.2	C9—C10—C11	114.17 (19)
C6—C5—H51	110.2	C9—C10—H101	122.9

C11—C10—H101	122.9	C107—C106—C114	111.66 (18)
C6—C11—C10	116.01 (18)	C111—C106—C114	113.8 (2)
C6—C11—H111	122.0	C106—C107—O115	111.75 (16)
C10—C11—H111	122.0	C106—C107—C108	110.21 (16)
C3—C12—H121	109.5	O115—C107—C108	108.99 (17)
C3—C12—H122	109.5	C106—C107—H1071	108.6
H121—C12—H122	109.5	O115—C107—H1071	108.6
C3—C12—H123	109.5	C108—C107—H1071	108.6
H121—C12—H123	109.5	C107—C108—C109	110.00 (17)
H122—C12—H123	109.5	C107—C108—C116	112.71 (18)
C3—C13—H131	109.5	C109—C108—C116	109.88 (18)
C3—C13—H132	109.5	C107—C108—H1081	108.0
H131—C13—H132	109.5	C109—C108—H1081	108.0
C3—C13—H133	109.5	C116—C108—H1081	108.0
H131—C13—H133	109.5	C101—C109—C108	106.76 (17)
H132—C13—H133	109.5	C101—C109—C110	107.97 (19)
C6—C14—H141	109.5	C108—C109—C110	106.70 (18)
C6—C14—H142	109.5	C101—C109—H1091	111.7
H141—C14—H142	109.5	C108—C109—H1091	111.7
C6—C14—H143	109.5	C110—C109—H1091	111.7
H141—C14—H143	109.5	C109—C110—C111	114.8 (2)
H142—C14—H143	109.5	C109—C110—H1101	122.6
C8—C16—O18	110.45 (19)	C111—C110—H1101	122.6
C8—C16—O17	126.3 (2)	C106—C111—C110	115.77 (19)
O18—C16—O17	123.3 (2)	C106—C111—H1111	122.1
O18—C19—H191	109.5	C110—C111—H1111	122.1
O18—C19—H192	109.5	C103—C112—H1121	109.5
H191—C19—H192	109.5	C103—C112—H1122	109.5
O18—C19—H193	109.5	H1121—C112—H1122	109.5
H191—C19—H193	109.5	C103—C112—H1123	109.5
H192—C19—H193	109.5	H1121—C112—H1123	109.5
O102—C101—C105	104.94 (18)	H1122—C112—H1123	109.5
O102—C101—C109	109.86 (18)	C103—C113—H1131	109.5
C105—C101—C109	110.00 (17)	C103—C113—H1132	109.5
O102—C101—H1011	110.6	H1131—C113—H1132	109.5
C105—C101—H1011	110.6	C103—C113—H1133	109.5
C109—C101—H1011	110.6	H1131—C113—H1133	109.5
O102—C103—O104	105.97 (19)	H1132—C113—H1133	109.5
O102—C103—C112	110.7 (3)	C106—C114—H1141	109.5
O104—C103—C112	110.3 (2)	C106—C114—H1142	109.5
O102—C103—C113	108.3 (3)	H1141—C114—H1142	109.5
O104—C103—C113	107.3 (2)	C106—C114—H1143	109.5
C112—C103—C113	113.9 (2)	H1141—C114—H1143	109.5
C101—C105—O104	104.90 (18)	H1142—C114—H1143	109.5
C101—C105—C106	110.81 (18)	C108—C116—O118	110.6 (2)
O104—C105—C106	109.82 (18)	C108—C116—O117	126.2 (2)
C101—C105—H1051	110.4	O118—C116—O117	123.2 (2)
O104—C105—H1051	110.4	O118—C119—H1191	109.5
C106—C105—H1051	110.4	O118—C119—H1192	109.5
C105—C106—C107	104.25 (17)	H1191—C119—H1192	109.5
C105—C106—C111	106.91 (17)	O118—C119—H1193	109.5
C107—C106—C111	108.40 (17)	H1191—C119—H1193	109.5
C105—C106—C114	111.32 (19)	H1192—C119—H1193	109.5

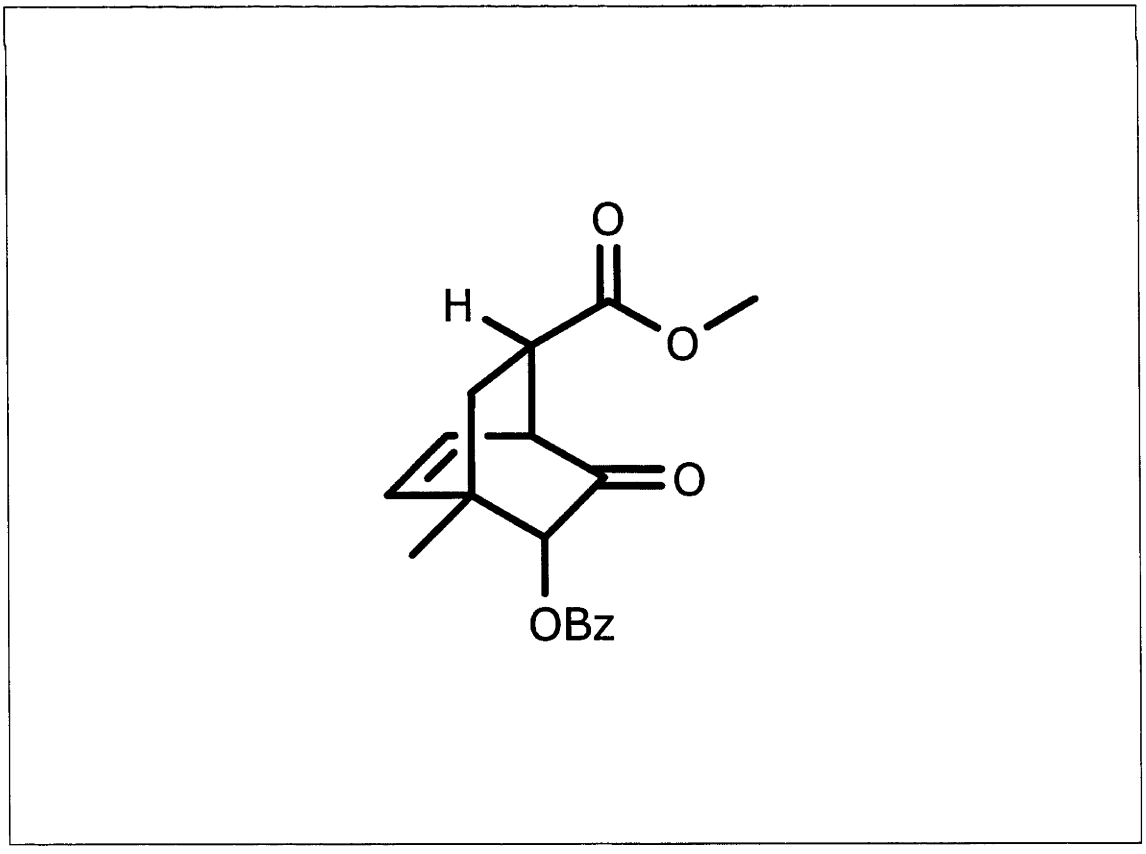
O2—C1—C5—O4	2.1 (2)	C3—O2—C1—C9	−139.1 (2)
O2—C1—C5—C6	−117.1 (2)	C3—O4—C5—C6	136.9 (2)
O2—C1—C9—C8	174.9 (2)	C5—O4—C3—C12	88.8 (2)
O2—C1—C9—C10	60.1 (2)	C5—O4—C3—C13	−146.1 (2)
O2—C3—O4—C5	−30.9 (2)	C5—C1—C9—C8	59.9 (2)
O4—C3—O2—C1	32.2 (2)	C5—C1—C9—C10	−55.0 (2)
O4—C5—C1—C9	120.6 (2)	C5—C6—C7—C8	63.5 (2)
O4—C5—C6—C7	−178.4 (2)	C5—C6—C11—C10	−56.1 (3)
O4—C5—C6—C11	−63.8 (2)	C6—C5—C1—C9	1.4 (2)
O4—C5—C6—C14	61.2 (2)	C6—C7—C8—C9	−3.8 (2)
O15—C7—C6—C5	−176.1 (2)	C6—C7—C8—C16	−126.5 (2)
O15—C7—C6—C11	69.7 (2)	C6—C11—C10—C9	0.9 (3)
O15—C7—C6—C14	−56.1 (2)	C7—C6—C11—C10	55.7 (3)
O15—C7—C8—C9	−125.9 (2)	C7—C8—C9—C10	57.4 (2)
O15—C7—C8—C16	111.3 (2)	C8—C7—C6—C11	−50.7 (2)
O17—C16—O18—C19	1.8 (4)	C8—C7—C6—C14	−176.5 (2)
O17—C16—C8—C7	27.0 (4)	C8—C9—C10—C11	−58.6 (2)
O17—C16—C8—C9	−95.9 (3)	C8—C16—O18—C19	−176.3 (3)
O18—C16—C8—C7	−155.0 (2)	C10—C9—C8—C16	−177.1 (2)
O18—C16—C8—C9	82.2 (2)	C10—C11—C6—C14	−179.6 (2)
O102—C101—C105—O104	1.0 (2)	C101—O102—C103—C112	−91.7 (2)
O102—C101—C105—C106	−117.4 (2)	C101—O102—C103—C113	142.7 (2)
O102—C101—C109—C108	174.9 (2)	C101—C105—O104—C103	15.9 (3)
O102—C101—C109—C110	60.5 (2)	C101—C105—C106—C107	−62.1 (2)
O102—C103—O104—C105	−27.2 (3)	C101—C105—C106—C111	52.6 (3)
O104—C103—O102—C101	27.9 (3)	C101—C105—C106—C114	177.4 (2)
O104—C105—C101—C109	119.1 (2)	C101—C109—C108—C107	−58.4 (2)
O104—C105—C106—C107	−177.5 (2)	C101—C109—C108—C116	66.2 (2)
O104—C105—C106—C111	−62.8 (2)	C101—C109—C110—C111	56.9 (2)
O104—C105—C106—C114	62.0 (3)	C103—O102—C101—C105	−17.6 (3)
O115—C107—C106—C105	−175.4 (2)	C103—O102—C101—C109	−135.8 (2)
O115—C107—C106—C111	71.0 (2)	C103—O104—C105—C106	135.0 (2)
O115—C107—C106—C114	−55.1 (2)	C105—O104—C103—C112	92.7 (3)
O115—C107—C108—C109	−126.8 (2)	C105—O104—C103—C113	−142.8 (3)
O115—C107—C108—C116	110.2 (2)	C105—C101—C109—C108	59.9 (3)
O117—C116—O118—C119	−0.4 (3)	C105—C101—C109—C110	−54.5 (3)
O117—C116—C108—C107	23.8 (3)	C105—C106—C107—C108	63.3 (2)
O117—C116—C108—C109	−99.2 (2)	C105—C106—C111—C110	−56.1 (3)
O118—C116—C108—C107	−158.2 (2)	C106—C105—C101—C109	0.7 (3)
O118—C116—C108—C109	78.7 (2)	C106—C107—C108—C109	−3.8 (2)
C1—O2—C3—C12	−87.7 (2)	C106—C107—C108—C116	−126.8 (2)
C1—O2—C3—C13	147.5 (2)	C106—C111—C110—C109	0.5 (3)
C1—C5—O4—C3	17.6 (2)	C107—C106—C111—C110	55.8 (2)
C1—C5—C6—C7	−62.7 (2)	C107—C108—C109—C110	56.9 (2)
C1—C5—C6—C11	51.9 (2)	C108—C107—C106—C111	−50.4 (2)
C1—C5—C6—C14	176.9 (2)	C108—C107—C106—C114	−176.5 (2)
C1—C9—C8—C7	−58.7 (2)	C108—C109—C110—C111	−57.6 (2)
C1—C9—C8—C16	66.8 (2)	C108—C116—O118—C119	−178.4 (2)
C1—C9—C10—C11	56.5 (3)	C110—C109—C108—C116	−178.5 (2)
C3—O2—C1—C5	−20.9 (2)	C110—C111—C106—C114	−179.4 (2)

Table *S4. Contact distances (Å)*

O2···C113^{i}	3.467 (3)	O17···C111	3.435 (3)
O4···C9^{ii}	3.494 (2)	O18···C5^{iv}	3.583 (3)
O15···O115	2.802 (2)	O115···C14^{iii}	3.413 (3)
O15···O115^{iii}	2.839 (2)	O115···C7	3.509 (3)
O15···C114^{iv}	3.572 (3)	O117···C10^{vi}	3.418 (3)
O17···C19^{v}	3.331 (3)	O117···C13^{vii}	3.444 (4)
O17···C110	3.368 (3)	C1···C113^{i}	3.562 (4)

Symmetry codes: (i) $1-x, \frac{1}{2}+y, 1-z$; (ii) $x, y-1, z$; (iii) $-x, \frac{1}{2}+y, 1-z$; (iv) $x, 1+y, z$; (v) $1-x, y-\frac{1}{2}, 1-z$; (vi) $-x, y-\frac{1}{2}, 1-z$; (vii) $x, y, 1+z$.

A.7 X-ray crystal structure report for compound 160a



Sample: ban0712

Compound: $C_{18}H_{18}O_5$

X-ray Structure Report

for

Christine Dietinger and Martin G. Banwell

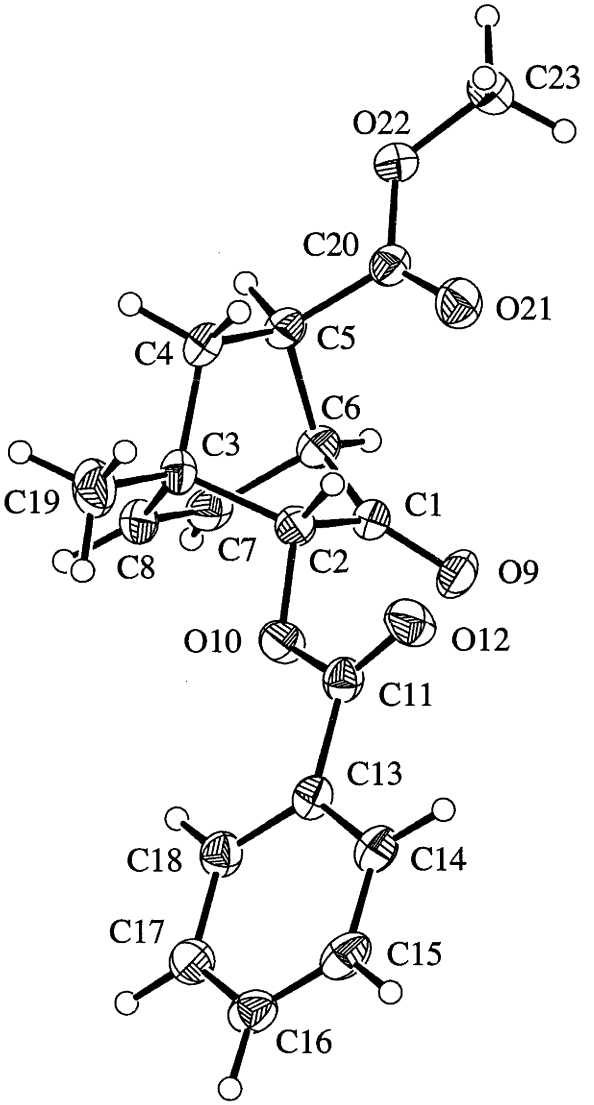
by

Anthony C. Willis

Research School of Chemistry,

The Australian National University, Canberra, ACT 0200, Australia

Monday, 5th February, 2007


C23
O22
C20
O21
C5
C4
C6
C3
C19
C1
C7
C8
C2
O9
O10
O12
C11
C13
C18
C14
C17
C15
C16

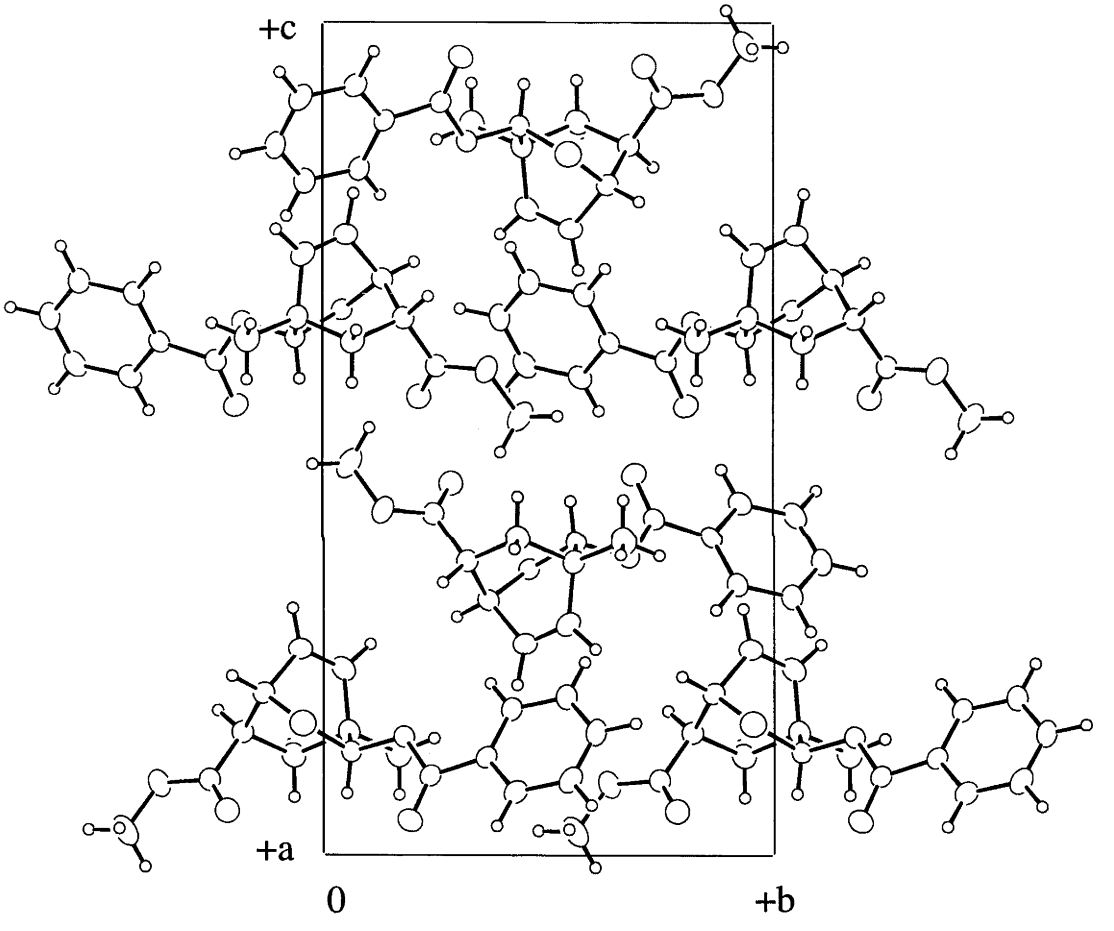

+c
+a
0
+b

Figure Captions for $C_{18}H_{18}O_5$

Figure 1. Molecular structure of $C_{18}H_{18}O_5$ with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

Figure 2. Unit cell packing diagram of $C_{18}H_{18}O_5$ projected down the *a* axis. Hydrogen atoms are drawn as circles with small radii.

Assignment of Chiral Centres

C2	R	C3	S	C5	R	C6	S

Calculated by PLATON.
Spek, A.L. (2001). PLATON - A Multipurpose Crystallographic Tool, Utrecht University, Utrecht, The Netherlands.

5 Feb 2007

Crystal structure of $C_{18}H_{18}O_5$ –ban0712

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Abstract

The crystal structure of $C_{18}H_{18}O_5$ is reported.

Comment

The compound is enantiometrically pure but the anomolous dispersion terms are very low for all elements in the structure and so the absolute configuration can not be determined in this experiment. Consequently Friedel-pair reflections have been averaged and the Flack parameter has not been refined. The absolute configuration of the molecule has been assigned on the basis of the synthetic precursors.

The crystallographic asymmetric unit consists of one molecule of $C_{18}H_{18}O_5$.

The final difference electron density map is essentially featureless.

Experimental

The compound was prepared by CD and recrystallized from hexane. The sample ID is 3CD68*p*8–12recryst.

Crystal data

$C_{18}H_{18}O_5$

$M_r = 314.34$

Orthorhombic

$P2_12_12_1$

$a = 7.3602\,(1)$ Å

$b = 10.7522\,(3)$ Å

$c = 19.9583\,(5)$ Å

$V = 1579.47\,(6)$ Å^3

$Z = 4$

$D_x = 1.322$ Mg m^{-3}

D_m not measured

Mo $K\alpha$ radiation

$\lambda = 0.71073$ Å

Cell parameters from 46702 reflections

$\theta = 3$–$27°$

$\mu = 0.096$ mm^{-1}

$T = 200$ K

Needle

Colourless

0.51 × 0.10 × 0.08 mm

Crystal source: local

Data collection

Nonius KappaCCD diffractometer

φ and ω scans with CCD

Absorption correction:

by integration *via* Gaussian method (Coppens, 1970) implemented in maXus (2000)

$T_{min} = 0.974$, $T_{max} = 0.994$

26114 measured reflections

2077 independent reflections

1463 reflections with

$I > 2.0\sigma(I)$

$R_{int} = 0.044$

$\theta_{max} = 27.472°$

$h = -8 \rightarrow 9$

$k = -13 \rightarrow 13$

$l = -25 \rightarrow 25$

Refinement

Refinement on F

$R = 0.0314$

$wR = 0.0351$

$S = 1.1518$

1463 reflections

208 parameters

H-atom parameters not refined

Method, part 1, Chebychev polynomial, (Carruthers & Watkin, 1979, Prince, 1982) [weight] = $1.0/[A_0{*}T_0(x) + A_1{*}T_1(x) \ldots + A_{n-1}]{*}T_{n-1}(x)]$ where A_i are the Chebychev coefficients listed below and x= Fcalc/Fmax Method = Robust Weighting (Prince, 1982) W = [weight] * [1-(deltaF/6*sigmaF)^2]^2 A_i are: 0.631 0.382 0.367

$(\Delta/\sigma)_{max} = 0.000215$

$\Delta\rho_{max} = 0.11$ e Å^{-3}

$\Delta\rho_{min} = -0.14$ e Å^{-3}

Extinction correction: none

Scattering factors from International Tables Vol C 4.2.6.8 and 6.1.1.4

Table 1. *Selected geometric parameters (Å, °)*

O9—C1	1.206 (2)	C4—C5	1.552 (3)
O10—C2	1.438 (2)	C5—C6	1.553 (3)
O10—C11	1.358 (2)	C5—C20	1.504 (3)
O12—C11	1.201 (2)	C6—C7	1.515 (3)
O21—C20	1.206 (2)	C7—C8	1.324 (3)
O22—C20	1.326 (2)	C11—C13	1.481 (3)
O22—C23	1.454 (3)	C13—C14	1.397 (3)
C1—C2	1.521 (3)	C13—C18	1.387 (3)
C1—C6	1.516 (3)	C14—C15	1.385 (3)
C2—C3	1.544 (3)	C15—C16	1.387 (3)
C3—C4	1.544 (3)	C16—C17	1.382 (3)
C3—C8	1.512 (3)	C17—C18	1.389 (3)
C3—C19	1.524 (3)		
C2—O10—C11	117.05 (15)	C5—C6—C7	107.71 (16)
C20—O22—C23	115.81 (19)	C1—C6—C7	102.86 (16)
O9—C1—C2	123.1 (2)	C6—C7—C8	114.63 (18)
O9—C1—C6	124.5 (2)	C3—C8—C7	115.95 (19)
C2—C1—C6	112.13 (16)	O10—C11—O12	122.90 (19)
C1—C2—O10	109.14 (15)	O10—C11—C13	112.00 (17)
C1—C2—C3	109.47 (16)	O12—C11—C13	125.06 (18)
O10—C2—C3	109.64 (16)	C11—C13—C14	117.22 (18)
C2—C3—C4	105.02 (16)	C11—C13—C18	123.02 (18)
C2—C3—C8	106.89 (16)	C14—C13—C18	119.7 (2)
C4—C3—C8	107.37 (18)	C13—C14—C15	120.2 (2)
C2—C3—C19	112.10 (19)	C14—C15—C16	119.9 (2)
C4—C3—C19	111.14 (18)	C15—C16—C17	119.9 (2)
C8—C3—C19	113.81 (19)	C16—C17—C18	120.7 (2)
C3—C4—C5	111.06 (16)	C17—C18—C13	119.7 (2)
C4—C5—C6	109.17 (16)	C5—C20—O22	111.50 (17)
C4—C5—C20	109.66 (17)	C5—C20—O21	124.02 (19)
C6—C5—C20	110.44 (16)	O22—C20—O21	124.5 (2)
C5—C6—C1	109.92 (16)		

All H atoms were observed in difference electron density maps prior to their inclusion. They were added at calculated positions and, during refinement, each rides on the C atom to which it is attached.

Data collection: *COLLECT* (Nonius BV, 1997). Cell refinement: Denzo/Scalepack (Otwinowski & Minor, 1997). Data reduction: Denzo/Scalepack (Otwinowski & Minor, 1997). Program(s) used to solve structure: *SIR*92 (Altomare *et al.* 1994). Program(s) used to refine structure: *CRYSTALS* (Watkin *et al.*2003). Molecular graphics: *ORTEP*–II (Johnson 1976) in teXsan (MSC, 1992–1997) . Software used to prepare material for publication: *CRYSTALS* (Watkin *et al.*2003).

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Supplementary data

Table *S*1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å²)*

$$U_{\mathrm{eq}} = (1/3)\Sigma_i\Sigma_j U^{ij} a^i a^j \mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	U_{eq}
O9	0.00875 (18)	0.45364 (16)	0.34283 (8)	0.0543
O10	0.2008 (2)	0.67902 (13)	0.35808 (7)	0.0475
O12	0.0640 (2)	0.69219 (14)	0.45859 (8)	0.0608
O21	0.2518 (2)	0.28575 (14)	0.44765 (8)	0.0576
O22	0.4431 (2)	0.13503 (14)	0.41540 (8)	0.0540
C1	0.1725 (2)	0.45724 (18)	0.34350 (10)	0.0394
C2	0.2797 (3)	0.56152 (19)	0.37649 (10)	0.0408
C3	0.4790 (3)	0.55642 (19)	0.35266 (11)	0.0455
C4	0.5546 (3)	0.4333 (2)	0.38116 (12)	0.0484
C5	0.4476 (3)	0.32003 (19)	0.35349 (11)	0.0435
C6	0.2945 (3)	0.3670 (2)	0.30628 (10)	0.0431
C7	0.3816 (3)	0.4485 (2)	0.25334 (10)	0.0489
C8	0.4748 (3)	0.5440 (2)	0.27721 (11)	0.0515
C11	0.0975 (3)	0.73722 (19)	0.40494 (10)	0.0431
C13	0.0389 (3)	0.8623 (2)	0.38266 (10)	0.0411
C14	−0.0802 (3)	0.9272 (2)	0.42440 (11)	0.0479
C15	−0.1275 (3)	1.0489 (2)	0.40970 (12)	0.0544
C16	−0.0588 (3)	1.1057 (2)	0.35267 (13)	0.0528
C17	0.0549 (3)	1.0403 (2)	0.31034 (12)	0.0511
C18	0.1045 (3)	0.91867 (19)	0.32501 (11)	0.0461
C19	0.5889 (4)	0.6674 (2)	0.37748 (14)	0.0676
C20	0.3684 (3)	0.24694 (19)	0.41073 (11)	0.0432
C23	0.3843 (4)	0.0598 (2)	0.47194 (14)	0.0691
H21	0.2751 (3)	0.55159 (19)	0.42628 (10)	0.0490
H41	0.5440 (3)	0.4347 (2)	0.43111 (12)	0.0580
H42	0.6853 (3)	0.4251 (2)	0.36823 (12)	0.0580
H51	0.5323 (3)	0.26550 (19)	0.32754 (11)	0.0522
H61	0.2242 (3)	0.2968 (2)	0.28609 (10)	0.0518
H71	0.3696 (3)	0.4315 (2)	0.20427 (10)	0.0587
H81	0.5386 (3)	0.6043 (2)	0.24717 (11)	0.0618
H141	−0.1316 (3)	0.8857 (2)	0.46504 (11)	0.0575
H151	−0.2110 (3)	1.0957 (2)	0.44014 (12)	0.0653
H161	−0.0915 (3)	1.1939 (2)	0.34221 (13)	0.0634
H171	0.1020 (3)	1.0809 (2)	0.26874 (12)	0.0613
H181	0.1870 (3)	0.87198 (19)	0.29416 (11)	0.0553
H191	0.7167 (4)	0.6604 (2)	0.36096 (14)	0.0810
H192	0.5885 (4)	0.6686 (2)	0.42758 (14)	0.0810
H193	0.5334 (4)	0.7460 (2)	0.36017 (14)	0.0810
H231	0.4483 (4)	−0.0222 (2)	0.47086 (14)	0.0829
H232	0.4140 (4)	0.1039 (2)	0.51468 (14)	0.0829
H233	0.2501 (4)	0.0461 (2)	0.46915 (14)	0.0829

Table *S*2. *Anisotropic displacement parameters* (Å²)

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O9	0.0306 (7)	0.0685 (10)	0.0637 (9)	0.0002 (7)	0.0023 (7)	0.0007 (9)
O10	0.0562 (9)	0.0415 (7)	0.0448 (7)	0.0080 (7)	0.0118 (7)	0.0011 (6)
O12	0.0719 (11)	0.0598 (9)	0.0507 (9)	0.0128 (9)	0.0207 (8)	0.0078 (7)
O21	0.0566 (9)	0.0574 (9)	0.0588 (9)	0.0048 (8)	0.0154 (8)	−0.0002 (8)
O22	0.0423 (7)	0.0479 (8)	0.0718 (9)	0.0060 (7)	−0.0004 (7)	0.0143 (8)
C1	0.0334 (9)	0.0424 (10)	0.0426 (10)	0.0002 (8)	0.0028 (8)	0.0026 (9)
C2	0.0396 (10)	0.0386 (9)	0.0441 (10)	0.0036 (9)	0.0049 (8)	0.0007 (8)
C3	0.0354 (9)	0.0453 (10)	0.0559 (12)	−0.0071 (9)	0.0036 (9)	0.0032 (10)
C4	0.0296 (9)	0.0570 (12)	0.0585 (12)	0.0000 (9)	−0.0006 (9)	0.0049 (10)
C5	0.0367 (9)	0.0459 (10)	0.0480 (10)	0.0070 (8)	0.0040 (9)	−0.0001 (9)
C6	0.0400 (10)	0.0452 (10)	0.0443 (10)	0.0030 (9)	0.0005 (8)	−0.0038 (9)
C7	0.0481 (11)	0.0571 (12)	0.0416 (10)	0.0137 (10)	0.0089 (9)	0.0008 (10)

C8	0.0419 (11)	0.0565 (12)	0.0561 (12)	0.0044 (11)	0.0158 (9)	0.0127 (10)
C11	0.0408 (10)	0.0436 (10)	0.0447 (11)	−0.0003 (9)	0.0066 (9)	−0.0047 (9)
C13	0.0357 (9)	0.0424 (10)	0.0453 (10)	−0.0014 (8)	0.0014 (8)	−0.0069 (9)
C14	0.0384 (10)	0.0536 (12)	0.0517 (11)	0.0033 (9)	0.0033 (9)	−0.0082 (9)
C15	0.0420 (10)	0.0539 (12)	0.0673 (14)	0.0104 (10)	−0.0029 (10)	−0.0173 (12)
C16	0.0458 (10)	0.0409 (10)	0.0718 (14)	0.0026 (9)	−0.0111 (12)	−0.0058 (10)
C17	0.0478 (11)	0.0443 (11)	0.0612 (12)	−0.0007 (10)	−0.0008 (10)	−0.0009 (10)
C18	0.0430 (10)	0.0421 (10)	0.0532 (11)	−0.0001 (9)	0.0053 (9)	−0.0049 (9)
C19	0.0578 (15)	0.0629 (15)	0.0820 (17)	−0.0240 (13)	0.0000 (13)	0.0015 (13)
C20	0.0363 (9)	0.0442 (11)	0.0490 (10)	0.0000 (8)	−0.0034 (9)	0.0009 (9)
C23	0.0571 (14)	0.0629 (15)	0.0873 (18)	−0.0063 (13)	−0.0042 (13)	0.0303 (13)

Table *S*3. *Geometric parameters (Å, °)*

O9—C1	1.206 (2)	C7—C8	1.324 (3)
O10—C2	1.438 (2)	C7—H71	1.000
O10—C11	1.358 (2)	C8—H81	1.000
O12—C11	1.201 (2)	C11—C13	1.481 (3)
O21—C20	1.206 (2)	C13—C14	1.397 (3)
O22—C20	1.326 (2)	C13—C18	1.387 (3)
O22—C23	1.454 (3)	C14—C15	1.385 (3)
C1—C2	1.521 (3)	C14—H141	1.000
C1—C6	1.516 (3)	C15—C16	1.387 (3)
C2—C3	1.544 (3)	C15—H151	1.000
C2—H21	1.000	C16—C17	1.382 (3)
C3—C4	1.544 (3)	C16—H161	1.000
C3—C8	1.512 (3)	C17—C18	1.389 (3)
C3—C19	1.524 (3)	C17—H171	1.000
C4—C5	1.552 (3)	C18—H181	1.000
C4—H41	1.000	C19—H191	1.000
C4—H42	1.000	C19—H192	1.000
C5—C6	1.553 (3)	C19—H193	1.000
C5—C20	1.504 (3)	C23—H231	1.000
C5—H51	1.000	C23—H232	1.000
C6—C7	1.515 (3)	C23—H233	1.000
C6—H61	1.000		

C2—O10—C11	117.05 (15)
C20—O22—C23	115.81 (19)
O9—C1—C2	123.1 (2)
O9—C1—C6	124.5 (2)
C2—C1—C6	112.13 (16)
C1—C2—O10	109.14 (15)
C1—C2—C3	109.47 (16)
O10—C2—C3	109.64 (16)
C1—C2—H21	109.5
O10—C2—H21	109.5
C3—C2—H21	109.5
C2—C3—C4	105.02 (16)
C2—C3—C8	106.89 (16)
C4—C3—C8	107.37 (18)
C2—C3—C19	112.10 (19)
C4—C3—C19	111.14 (18)
C8—C3—C19	113.81 (19)
C3—C4—C5	111.06 (16)
C3—C4—H41	109.1
C5—C4—H41	109.1
C3—C4—H42	109.1
C5—C4—H42	109.1
H41—C4—H42	109.5
C4—C5—C6	109.17 (16)
C4—C5—C20	109.66 (17)
C6—C5—C20	110.44 (16)
C4—C5—H51	109.2
C6—C5—H51	109.2
C20—C5—H51	109.2
C5—C6—C1	109.92 (16)
C5—C6—C7	107.71 (16)
C1—C6—C7	102.86 (16)
C5—C6—H61	112.0
C1—C6—H61	112.0
C7—C6—H61	112.0
C6—C7—C8	114.63 (18)
C6—C7—H71	122.7
C8—C7—H71	122.7
C3—C8—C7	115.95 (19)

C3—C8—H81	122.0
C7—C8—H81	122.0
O10—C11—O12	122.90 (19)
O10—C11—C13	112.00 (17)
O12—C11—C13	125.06 (18)
C11—C13—C14	117.22 (18)
C11—C13—C18	123.02 (18)
C14—C13—C18	119.7 (2)
C13—C14—C15	120.2 (2)
C13—C14—H141	119.9
C15—C14—H141	119.9
C14—C15—C16	119.9 (2)
C14—C15—H151	120.1
C16—C15—H151	120.1
C15—C16—C17	119.9 (2)
C15—C16—H161	120.1
C17—C16—H161	120.1
C16—C17—C18	120.7 (2)
C16—C17—H171	119.7
C18—C17—H171	119.7
C17—C18—C13	119.7 (2)
C17—C18—H181	120.2
C13—C18—H181	120.2
C3—C19—H191	109.5
C3—C19—H192	109.5
H191—C19—H192	109.5
C3—C19—H193	109.5
H191—C19—H193	109.5
H192—C19—H193	109.5
C5—C20—O22	111.50 (17)
C5—C20—O21	124.02 (19)
O22—C20—O21	124.5 (2)
O22—C23—H231	109.5
O22—C23—H232	109.5
H231—C23—H232	109.5
O22—C23—H233	109.5
H231—C23—H233	109.5
H232—C23—H233	109.5

O9—C1—C2—O10	−45.2 (3)
O9—C1—C2—C3	−165.2 (2)
O9—C1—C6—C5	−133.0 (2)
O9—C1—C6—C7	112.5 (2)
O10—C2—C1—C6	129.2 (2)
O10—C2—C3—C4	174.4 (2)
O10—C2—C3—C8	−71.7 (2)
O10—C2—C3—C19	53.7 (2)
O10—C11—C13—C14	175.0 (2)
O10—C11—C13—C18	−8.6 (3)
O12—C11—O10—C2	−3.5 (3)
O12—C11—C13—C14	−7.1 (3)
O12—C11—C13—C18	169.2 (2)
O21—C20—O22—C23	−3.8 (3)
O21—C20—C5—C4	66.1 (3)
O21—C20—C5—C6	−54.3 (3)
O22—C20—C5—C4	−113.8 (2)
O22—C20—C5—C6	125.8 (2)
C1—C2—O10—C11	103.6 (2)
C1—C2—C3—C4	−65.9 (2)
C1—C2—C3—C8	48.0 (2)
C1—C2—C3—C19	173.3 (2)
C1—C6—C5—C4	−56.7 (2)
C1—C6—C5—C20	64.0 (2)
C1—C6—C7—C8	58.8 (2)
C2—O10—C11—C13	174.4 (2)

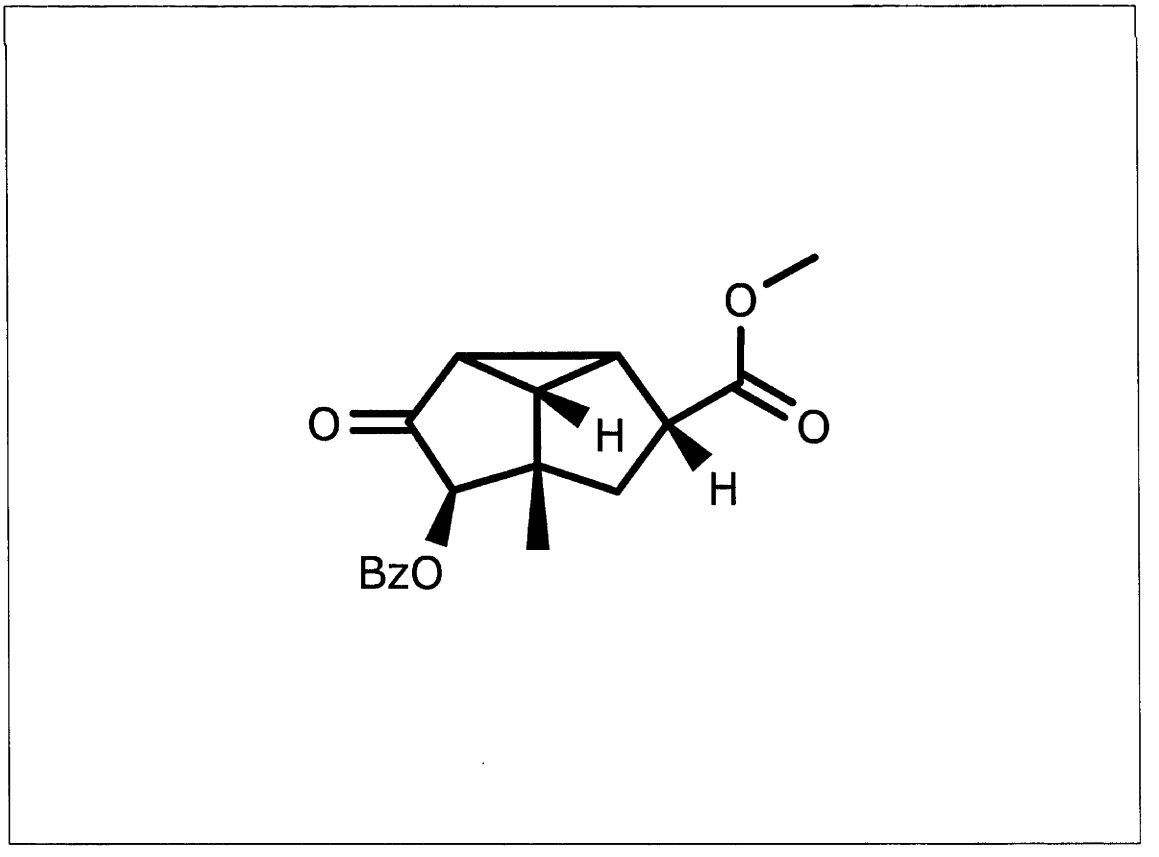
C2—C1—C6—C5	52.7 (2)
C2—C1—C6—C7	−61.7 (2)
C2—C3—C4—C5	60.9 (2)
C2—C3—C8—C7	−56.0 (2)
C3—C2—O10—C11	−136.5 (2)
C3—C2—C1—C6	9.1 (2)
C3—C4—C5—C6	−1.0 (2)
C3—C4—C5—C20	−122.1 (2)
C3—C8—C7—C6	−0.1 (3)
C4—C3—C8—C7	56.3 (3)
C4—C5—C6—C7	54.7 (2)
C5—C4—C3—C8	−52.6 (2)
C5—C4—C3—C19	−177.6 (2)
C5—C6—C7—C8	−57.2 (2)
C5—C20—O22—C23	176.1 (2)
C7—C6—C5—C20	175.3 (2)
C7—C8—C3—C19	179.7 (2)
C11—C13—C14—C15	174.1 (2)
C11—C13—C18—C17	−174.6 (2)
C13—C14—C15—C16	1.1 (3)
C13—C18—C17—C16	0.1 (3)
C14—C13—C18—C17	1.7 (3)
C14—C15—C16—C17	0.7 (3)
C15—C14—C13—C18	−2.4 (3)
C15—C16—C17—C18	−1.4 (3)

Table *S4. Contact distances (Å)*

O9···C17^{i}	3.230 (3)	O21···C15^{iv}	3.472 (3)
O9···C4^{ii}	3.436 (3)	O21···C16^{v}	3.545 (3)
O9···C18^{i}	3.472 (3)	O21···C23^{iii}	3.557 (3)
O12···C23^{iii}	3.319 (3)	O22···C15^{vi}	3.295 (3)
		C7···C17^{i}	3.593 (3)

Symmetry codes: (i) $-x, y-\frac{1}{2}, \frac{1}{2}-z$; (ii) $x-1, y, z$; (iii) $x-\frac{1}{2}, \frac{1}{2}-y, 1-z$; (iv) $\frac{1}{2}+x, \frac{3}{2}-y, 1-z$; (v) $x, y-1, z$; (vi) $1+x, y-1, z$.

A.8 X-ray crystal structure report for compound 169a



Sample: ban0725

Compound: $C_{18}H_{18}O_5$

X-ray Structure Report

for

Christine Dietinger and Martin G. Banwell

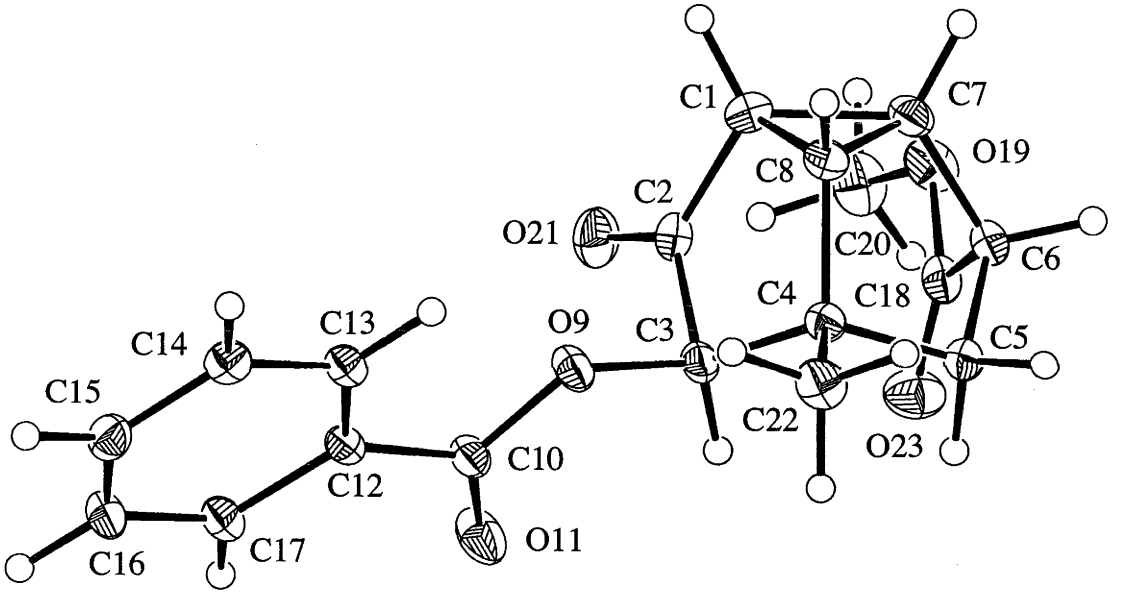
by

Anthony C. Willis

Research School of Chemistry,

The Australian National University, Canberra, ACT 0200, Australia

Monday, 21st May, 2007


C1
C7
O19
C8
C2
O21
C20
C6
C4
C18
C13
O9
C3
C5
C14
C15
C22
O23
C10
C12
O11
C16
C17

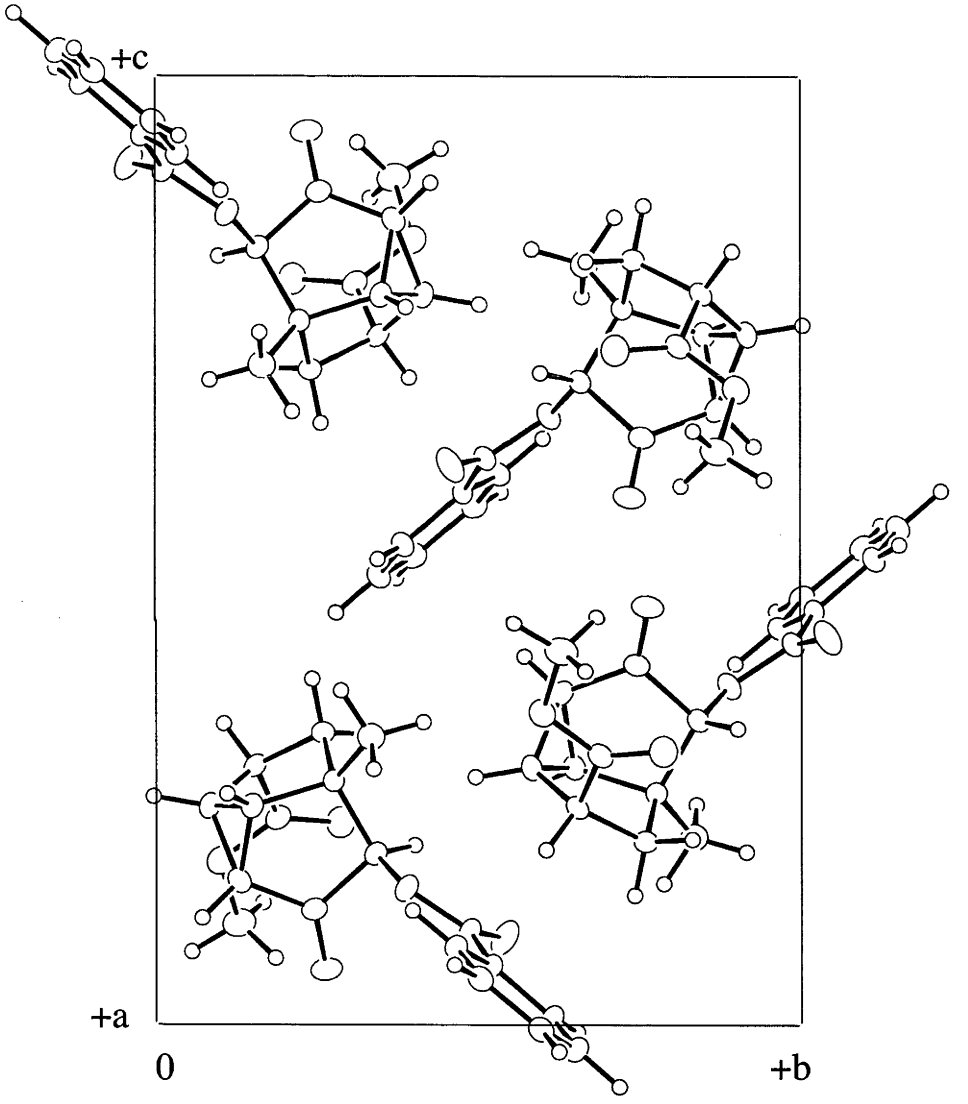

+c
+a
0
+b

Figure Captions for $C_{18}H_{18}O_5$

Figure 1. Molecular structure of $C_{18}H_{18}O_5$ with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

Figure 2. Unit cell packing diagram of $C_{18}H_{18}O_5$ projected down the *a* axis. Hydrogen atoms are drawn as circles with small radii.

Assignment of Chiral Centres

C1	R	C3	R	C4	S	C6	R
C7	R	C8	S				

Calculated by PLATON.
Spek, A.L. (2001). PLATON - A Multipurpose Crystallographic Tool, Utrecht University, Utrecht, The Netherlands.

Crystal structure of $C_{18}H_{18}O_5$ — ban0725

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Abstract

The crystal structure of $C_{18}H_{18}O_5$ is reported.

Comment

The compound is enantiometrically pure but the anomolous dispersion terms are very low for all elements in the structure and so the absolute configuration can not be determined in this experiment. Consequently Friedel-pair reflections have been averaged and the Flack parameter has not been refined. The absolute configuration of the molecule has been assigned on the basis of the synthetic precursors.

The crystallographic asymmetric unit consists of one molecule of $C_{18}H_{18}O_5$.

The final difference electron density map is essentially featureless with the largest peaks lying on C—C bonds.

Experimental

The compound was prepared by CD and recrystallized from hexane/benzene. The sample ID is 4CD47 + 49p13recryst.

Refinement

All hydrogen atoms were observed in difference electron density maps prior to their inclusion. They were added at calculated positions and, during refinement, each rides on the carbon atom to which it is attached.

Computing details

Data collection: *COLLECT* (Nonius BV, 1997); cell refinement: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *CRYSTALS* (Watkin *et al.* 2003); molecular graphics: *ORTEP*II (Johnson 1976) in *TEXSAN* (MSC, 1992-1997); software used to prepare material for publication: *CRYSTALS* (Watkin *et al.* 2003).

(ban0725)

Crystal data

$C_{18}H_{18}O_5$	$V = 1528.75\ (5)\ Å^3$
$M_r = 314.34$	$Z = 4$
Orthorhombic, $P2_12_12_1$	Mo $K\alpha$
$a = 8.0188\ (1)$ Å	$\mu = 0.10\ mm^{-1}$
$b = 11.3687\ (2)$ Å	$T = 200$ K
$c = 16.7694\ (4)$ Å	$0.40 \times 0.20 \times 0.09$ mm

Data collection

Nonius KappaCCD diffractometer	2020 independent reflections
Absorption correction: integration via Gaussian method (Coppens, 1970) implemented in maXus (2000)	1701 reflections with $I > 2.0\sigma(I)$
$T_{min} = 0.972$, $T_{max} = 0.991$	$R_{int} = 0.037$
21082 measured reflections	

Refinement

R = 0.029	$\Delta\rho_{max} = 0.15\ e\ Å^{-3}$
wR = 0.034	$\Delta\rho_{min} = -0.15\ e\ Å^{-3}$
$S = 1.13$	Absolute structure: from synthesis
1701 reflections	Flack parameter: ?
208 parameters	Rogers parameter: ?
H-atom parameters not refined	

Selected geometric parameters (Å, °)

C1—C2	1.485 (2)	C7—C8	1.489 (2)
C1—C7	1.536 (2)	O9—C10	1.3512 (17)
C1—C8	1.517 (2)	C10—O11	1.208 (2)
C2—C3	1.531 (2)	C10—C12	1.487 (2)
C2—O21	1.213 (2)	C12—C13	1.391 (2)
C3—C4	1.5409 (19)	C12—C17	1.4001 (19)
C3—O9	1.4540 (18)	C13—C14	1.389 (2)
C4—C5	1.545 (2)	C14—C15	1.390 (2)
C4—C8	1.5471 (19)	C15—C16	1.389 (3)
C4—C22	1.524 (2)	C16—C17	1.385 (2)
C5—C6	1.544 (2)	C18—O19	1.336 (2)
C6—C7	1.526 (2)	C18—O23	1.199 (2)
C6—C18	1.516 (2)	O19—C20	1.449 (2)
C2—C1—C7	118.59 (13)	C6—C7—C8	110.46 (13)
C2—C1—C8	107.87 (12)	C4—C8—C1	106.99 (12)
C7—C1—C8	58.36 (10)	C4—C8—C7	106.43 (13)
C1—C2—C3	108.94 (12)	C1—C8—C7	61.48 (11)
C1—C2—O21	126.33 (15)	C3—O9—C10	117.73 (11)

C3—C2—O21	124.55 (15)	O9—C10—O11	123.66 (14)
C2—C3—C4	105.65 (11)	O9—C10—C12	111.52 (12)
C2—C3—O9	103.93 (11)	O11—C10—C12	124.81 (13)
C4—C3—O9	108.92 (12)	C10—C12—C13	121.89 (12)
C3—C4—C5	108.47 (12)	C10—C12—C17	118.26 (14)
C3—C4—C8	104.85 (11)	C13—C12—C17	119.85 (15)
C5—C4—C8	103.15 (11)	C12—C13—C14	120.28 (14)
C3—C4—C22	113.85 (12)	C13—C14—C15	119.45 (15)
C5—C4—C22	112.36 (12)	C14—C15—C16	120.64 (15)
C8—C4—C22	113.34 (14)	C15—C16—C17	119.93 (14)
C4—C5—C6	106.71 (11)	C12—C17—C16	119.82 (16)
C5—C6—C7	103.71 (13)	C6—C18—O19	111.31 (13)
C5—C6—C18	113.51 (12)	C6—C18—O23	125.13 (15)
C7—C6—C18	113.00 (12)	O19—C18—O23	123.53 (15)
C1—C7—C6	119.09 (12)	C18—O19—C20	115.79 (14)
C1—C7—C8	60.16 (11)		

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supplementary materials

Crystal structure of $C_{18}H_{18}O_5$ — ban0725

Christine Dietinger, Martin G. Banwell and Anthony C. Willis

(ban0725)

Crystal data

$C_{18}H_{18}O_5$	$D_x = 1.366$ Mg m^{-3}
$M_r = 314.34$	Mo $K\alpha$ radiation $\lambda = 0.71073$ Å
Orthorhombic, $P2_12_12_1$	Cell parameters from 12481 reflections
$a = 8.0188$ (1) Å	$\theta = 2.6$–$27.5°$
$b = 11.3687$ (2) Å	$\mu = 0.10$ mm^{-1}
$c = 16.7694$ (4) Å	$T = 200$ K
$V = 1528.75$ (5) Å^3	Plate, colourless
$Z = 4$	0.40 × 0.20 × 0.09 mm
$F_{000} = 664$	

Data collection

Nonius KappaCCD diffractometer	1701 reflections with $I > 2.0\sigma(I)$
Monochromator: graphite	$R_{int} = 0.037$
$T = 200$ K	$\theta_{max} = 27.5°$
φ and ω scans with CCD	$\theta_{min} = 2.8°$
Absorption correction: integration via Gaussian method (Coppens, 1970) implemented in maXus (2000)	$h = -9 \rightarrow 10$
$T_{min} = 0.972$, $T_{max} = 0.991$	$k = -14 \rightarrow 14$
21082 measured reflections	$l = -19 \rightarrow 21$
2020 independent reflections	

Refinement

Refinement on F	H-atom parameters not refined
Least-squares matrix: full	Method, part 1, Chebychev polynomial, (Carruthers & Watkin, 1979, *P*rince, 1982) [*w*eight] = 1.0/ $[A_0*T_0(x) + A_1*T_1(x) \cdots + A_{n-1}]*T_{n-1}(x)]$ where A_i are the Chebychev coefficients listed below and x = F /Fmax Method = Robust Weighting (*P*rince, 1982) W = [*w*eight] * [1-(delta$F$/6*sigma$F$)^2]^2 A_i are: 0.928 0.588 0.675
R = 0.029	$(\Delta/\sigma)_{max} = 0.0003$
wR = 0.034	$\Delta\rho_{max} = 0.15$ e Å^{-3}
$S = 1.13$	$\Delta\rho_{min} = -0.15$ e Å^{-3}
1701 reflections	Extinction correction: None

208 parameters	Absolute structure: from synthesis
Primary atom site location: structure-invariant direct methods	Flack parameter: ?
Hydrogen site location: inferred from neighbouring sites	Rogers parameter: ?

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters ($Å^2$)

	x	y	z	U_{iso}*/U_{eq}
C1	0.2515 (2)	0.12910 (14)	0.15071 (9)	0.0339
C2	0.1941 (2)	0.24526 (14)	0.12097 (9)	0.0310
C3	0.25025 (19)	0.34080 (13)	0.17948 (8)	0.0275
C4	0.29854 (19)	0.27546 (12)	0.25660 (8)	0.0272
C5	0.1399 (2)	0.25902 (13)	0.30767 (8)	0.0304
C6	0.0444 (2)	0.15351 (13)	0.27196 (8)	0.0295
C7	0.1797 (2)	0.08276 (13)	0.22963 (9)	0.0323
C8	0.3401 (2)	0.14873 (13)	0.22948 (9)	0.0311
O9	0.40023 (14)	0.38874 (9)	0.14317 (7)	0.0314
C10	0.38467 (19)	0.48728 (13)	0.09875 (9)	0.0287
O11	0.25558 (17)	0.54088 (11)	0.09134 (9)	0.0457
C12	0.5463 (2)	0.52191 (12)	0.06210 (8)	0.0259
C13	0.6949 (2)	0.46576 (13)	0.08154 (8)	0.0289
C14	0.8444 (2)	0.50328 (14)	0.04828 (9)	0.0322
C15	0.8440 (2)	0.59700 (14)	−0.00500 (9)	0.0346
C16	0.6958 (2)	0.65200 (14)	−0.02600 (10)	0.0370
C17	0.5467 (2)	0.61471 (13)	0.00721 (9)	0.0326
C18	−0.0970 (2)	0.18917 (14)	0.21708 (9)	0.0315
O19	−0.14673 (18)	0.09911 (11)	0.17180 (7)	0.0419
C20	−0.2570 (3)	0.12865 (19)	0.10635 (11)	0.0478
O21	0.12443 (17)	0.26417 (12)	0.05802 (7)	0.0441
C22	0.4394 (2)	0.33388 (16)	0.30296 (10)	0.0392
O23	−0.15528 (18)	0.28606 (12)	0.21258 (8)	0.0477
H11	0.2997 (2)	0.07168 (14)	0.11188 (9)	0.0407*
H31	0.16265 (19)	0.40196 (13)	0.18855 (8)	0.0330*
H51	0.1710 (2)	0.24234 (13)	0.36431 (8)	0.0365*
H52	0.0694 (2)	0.33149 (13)	0.30539 (8)	0.0365*
H61	−0.0021 (2)	0.10511 (13)	0.31652 (8)	0.0354*
H71	0.1840 (2)	−0.00395 (13)	0.23946 (9)	0.0388*
H81	0.4489 (2)	0.11019 (13)	0.24235 (9)	0.0373*
H131	0.6941 (2)	0.39810 (13)	0.11964 (8)	0.0347*
H141	0.9513 (2)	0.46324 (14)	0.06255 (9)	0.0387*
H151	0.9516 (2)	0.62503 (14)	−0.02844 (9)	0.0415*
H161	0.6966 (2)	0.71847 (14)	−0.06506 (10)	0.0443*
H171	0.4397 (2)	0.65397 (13)	−0.00797 (9)	0.0391*
H201	−0.2867 (3)	0.05554 (19)	0.07637 (11)	0.0574*
H202	−0.3608 (3)	0.16573 (19)	0.12780 (11)	0.0574*
H203	−0.1997 (3)	0.18506 (19)	0.06972 (11)	0.0574*
H221	0.4640 (2)	0.28696 (16)	0.35201 (10)	0.0470*
H222	0.4052 (2)	0.41530 (16)	0.31850 (10)	0.0470*

H223	0.5415 (2)	0.33771 (16)	0.26879 (10)	0.0470*

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
C1	0.0396 (8)	0.0295 (7)	0.0327 (7)	0.0022 (7)	0.0033 (7)	−0.0064 (6)
C2	0.0308 (7)	0.0362 (8)	0.0259 (6)	−0.0020 (7)	0.0058 (6)	0.0031 (6)
C3	0.0269 (6)	0.0271 (7)	0.0285 (6)	0.0001 (6)	0.0044 (6)	0.0046 (6)
C4	0.0316 (7)	0.0239 (6)	0.0261 (6)	−0.0017 (6)	0.0003 (6)	−0.0001 (6)
C5	0.0369 (8)	0.0298 (7)	0.0244 (6)	−0.0012 (6)	0.0031 (6)	0.0006 (5)
C6	0.0332 (7)	0.0276 (7)	0.0277 (6)	−0.0020 (6)	0.0017 (6)	0.0070 (6)
C7	0.0377 (8)	0.0233 (6)	0.0360 (7)	0.0018 (6)	−0.0007 (6)	0.0041 (6)
C8	0.0337 (7)	0.0263 (6)	0.0334 (7)	0.0050 (6)	0.0007 (6)	0.0024 (6)
O9	0.0268 (5)	0.0293 (5)	0.0382 (5)	−0.0005 (4)	0.0042 (4)	0.0103 (5)
C10	0.0300 (7)	0.0251 (7)	0.0311 (7)	0.0004 (6)	0.0010 (6)	0.0061 (5)
O11	0.0313 (6)	0.0414 (6)	0.0645 (8)	0.0083 (6)	0.0076 (6)	0.0225 (6)
C12	0.0287 (6)	0.0217 (6)	0.0274 (6)	−0.0014 (5)	−0.0005 (6)	0.0020 (5)
C13	0.0305 (7)	0.0274 (6)	0.0288 (7)	−0.0010 (6)	−0.0016 (6)	0.0025 (6)
C14	0.0288 (7)	0.0345 (7)	0.0333 (7)	−0.0025 (6)	−0.0003 (6)	−0.0051 (6)
C15	0.0358 (8)	0.0346 (7)	0.0333 (7)	−0.0093 (7)	0.0069 (7)	−0.0052 (6)
C16	0.0484 (10)	0.0296 (7)	0.0328 (7)	−0.0066 (7)	0.0059 (7)	0.0062 (6)
C17	0.0373 (8)	0.0274 (7)	0.0329 (7)	0.0001 (6)	−0.0004 (6)	0.0066 (6)
C18	0.0299 (7)	0.0338 (8)	0.0309 (7)	−0.0020 (6)	0.0032 (6)	0.0069 (6)
O19	0.0465 (7)	0.0378 (6)	0.0414 (6)	−0.0049 (5)	−0.0127 (6)	0.0044 (5)
C20	0.0438 (10)	0.0587 (11)	0.0409 (8)	−0.0070 (9)	−0.0108 (8)	0.0049 (9)
O21	0.0504 (8)	0.0552 (8)	0.0268 (5)	−0.0051 (7)	−0.0037 (6)	0.0050 (5)
C22	0.0395 (9)	0.0401 (9)	0.0379 (8)	−0.0074 (7)	−0.0067 (7)	−0.0008 (7)
O23	0.0491 (7)	0.0416 (6)	0.0525 (7)	0.0134 (6)	−0.0110 (7)	0.0000 (6)

Geometric parameters (Å, °)

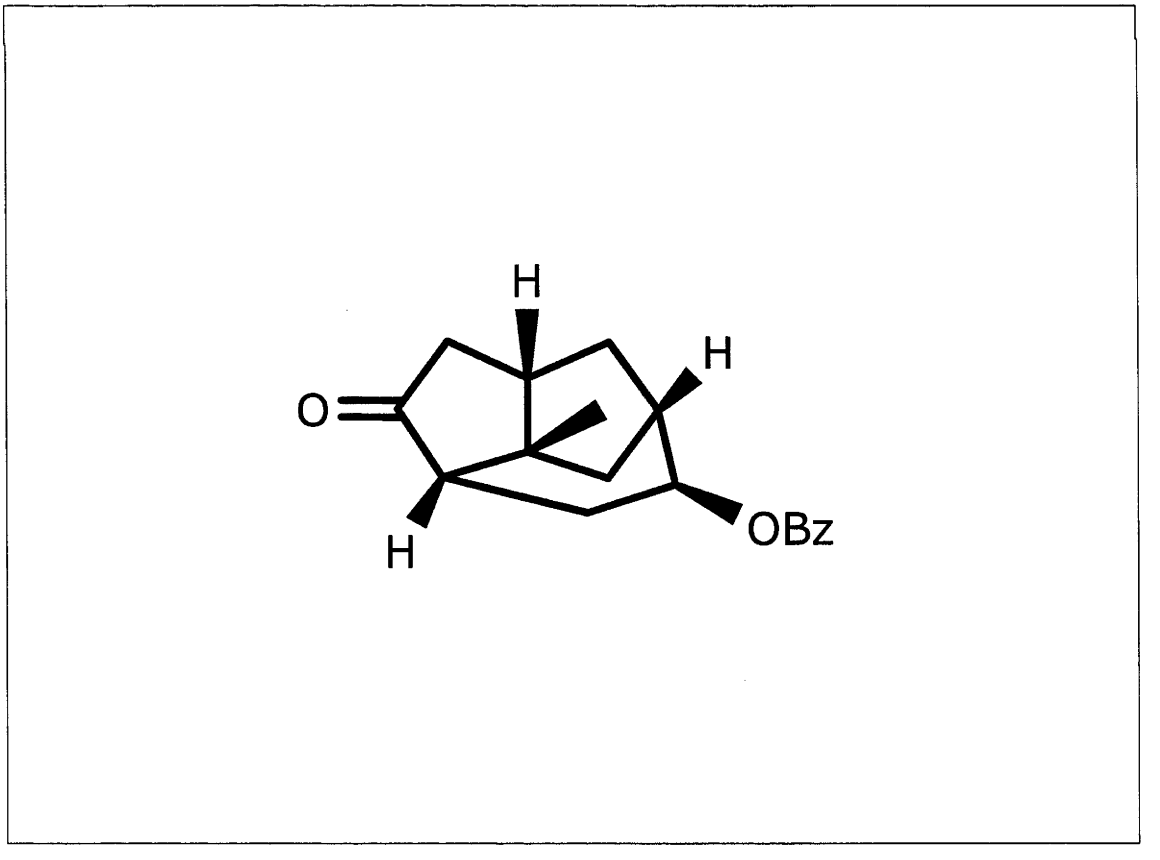
C1—C2	1.485 (2)	C10—O11	1.208 (2)
C1—C7	1.536 (2)	C10—C12	1.487 (2)
C1—C8	1.517 (2)	C12—C13	1.391 (2)
C1—H11	1.000	C12—C17	1.4001 (19)
C2—C3	1.531 (2)	C13—C14	1.389 (2)
C2—O21	1.213 (2)	C13—H131	1.000
C3—C4	1.5409 (19)	C14—C15	1.390 (2)
C3—O9	1.4540 (18)	C14—H141	1.000
C3—H31	1.000	C15—C16	1.389 (3)
C4—C5	1.545 (2)	C15—H151	1.000
C4—C8	1.5471 (19)	C16—C17	1.385 (2)
C4—C22	1.524 (2)	C16—H161	1.000
C5—C6	1.544 (2)	C17—H171	1.000
C5—H51	1.000	C18—O19	1.336 (2)
C5—H52	1.000	C18—O23	1.199 (2)
C6—C7	1.526 (2)	O19—C20	1.449 (2)
C6—C18	1.516 (2)	C20—H201	1.000
C6—H61	1.000	C20—H202	1.000

C7—C8	1.489 (2)	C20—H203	1.000
C7—H71	1.000	C22—H221	1.000
C8—H81	1.000	C22—H222	1.000
O9—C10	1.3512 (17)	C22—H223	1.000
O11···C14^{i}	3.402 (2)	O23···C13^{i}	3.232 (2)
O11···C6^{ii}	3.561 (2)	O23···C7^{ii}	3.515 (2)
O21···C20^{iii}	3.160 (2)	C6···C14^{v}	3.578 (2)
O21···C14^{i}	3.530 (2)	C7···C13^{v}	3.579 (2)
O21···C13^{iv}	3.554 (2)		
C2—C1—C7	118.59 (13)	C4—C8—H81	122.2
C2—C1—C8	107.87 (12)	C1—C8—H81	122.2
C7—C1—C8	58.36 (10)	C7—C8—H81	122.2
C2—C1—H11	118.8	C3—O9—C10	117.73 (11)
C7—C1—H11	118.8	O9—C10—O11	123.66 (14)
C8—C1—H11	118.8	O9—C10—C12	111.52 (12)
C1—C2—C3	108.94 (12)	O11—C10—C12	124.81 (13)
C1—C2—O21	126.33 (15)	C10—C12—C13	121.89 (12)
C3—C2—O21	124.55 (15)	C10—C12—C17	118.26 (14)
C2—C3—C4	105.65 (11)	C13—C12—C17	119.85 (15)
C2—C3—O9	103.93 (11)	C12—C13—C14	120.28 (14)
C4—C3—O9	108.92 (12)	C12—C13—H131	119.9
C2—C3—H31	112.6	C14—C13—H131	119.9
C4—C3—H31	112.6	C13—C14—C15	119.45 (15)
O9—C3—H31	112.6	C13—C14—H141	120.3
C3—C4—C5	108.47 (12)	C15—C14—H141	120.3
C3—C4—C8	104.85 (11)	C14—C15—C16	120.64 (15)
C5—C4—C8	103.15 (11)	C14—C15—H151	119.7
C3—C4—C22	113.85 (12)	C16—C15—H151	119.7
C5—C4—C22	112.36 (12)	C15—C16—C17	119.93 (14)
C8—C4—C22	113.34 (14)	C15—C16—H161	120.0
C4—C5—C6	106.71 (11)	C17—C16—H161	120.0
C4—C5—H51	110.2	C12—C17—C16	119.82 (16)
C6—C5—H51	110.2	C12—C17—H171	120.1
C4—C5—H52	110.2	C16—C17—H171	120.1
C6—C5—H52	110.2	C6—C18—O19	111.31 (13)
H51—C5—H52	109.5	C6—C18—O23	125.13 (15)
C5—C6—C7	103.71 (13)	O19—C18—O23	123.53 (15)
C5—C6—C18	113.51 (12)	C18—O19—C20	115.79 (14)
C7—C6—C18	113.00 (12)	O19—C20—H201	109.5
C5—C6—H61	108.8	O19—C20—H202	109.5
C7—C6—H61	108.8	H201—C20—H202	109.5
C18—C6—H61	108.8	O19—C20—H203	109.5
C1—C7—C6	119.09 (12)	H201—C20—H203	109.5
C1—C7—C8	60.16 (11)	H202—C20—H203	109.5
C6—C7—C8	110.46 (13)	C4—C22—H221	109.5
C1—C7—H71	117.9	C4—C22—H222	109.5
C6—C7—H71	117.9	H221—C22—H222	109.5

C8—C7—H71	117.9	C4—C22—H223	109.5
C4—C8—C1	106.99 (12)	H221—C22—H223	109.5
C4—C8—C7	106.43 (13)	H222—C22—H223	109.5
C1—C8—C7	61.48 (11)		
O9—C3—C2—O21	−76.5 (2)	C2—C3—O9—C10	96.4 (1)
O9—C3—C2—C1	98.7 (1)	C2—C3—C4—C5	−86.4 (1)
O9—C3—C4—C5	162.5 (1)	C2—C3—C4—C8	23.3 (2)
O9—C3—C4—C8	−87.8 (1)	C2—C3—C4—C22	147.8 (1)
O9—C3—C4—C22	36.7 (2)	C3—O9—C10—C12	−176.9 (1)
O9—C10—C12—C13	−7.7 (2)	C3—C2—C1—C7	64.8 (2)
O9—C10—C12—C17	173.0 (1)	C3—C2—C1—C8	1.7 (2)
O11—C10—O9—C3	4.3 (2)	C3—C4—C5—C6	79.4 (1)
O11—C10—C12—C13	171.1 (2)	C3—C4—C8—C7	−87.2 (1)
O11—C10—C12—C17	−8.2 (2)	C4—C3—O9—C10	−151.3 (1)
O19—C18—C6—C5	163.5 (1)	C4—C5—C6—C7	24.3 (1)
O19—C18—C6—C7	45.8 (2)	C4—C5—C6—C18	−98.7 (1)
O21—C2—C1—C7	−120.0 (2)	C4—C8—C1—C7	−99.8 (1)
O21—C2—C1—C8	176.8 (2)	C4—C8—C7—C6	−11.9 (2)
O21—C2—C3—C4	168.9 (2)	C5—C4—C8—C7	26.3 (1)
O23—C18—O19—C20	10.2 (2)	C5—C6—C7—C8	−7.6 (2)
O23—C18—C6—C5	−14.6 (2)	C6—C5—C4—C8	−31.4 (1)
O23—C18—C6—C7	−132.4 (2)	C6—C5—C4—C22	−153.8 (1)
C1—C2—C3—C4	−15.9 (2)	C6—C7—C1—C8	98.1 (1)
C1—C7—C6—C5	−74.0 (2)	C6—C18—O19—C20	−168.0 (1)
C1—C7—C6—C18	49.3 (2)	C7—C8—C4—C22	148.0 (1)
C1—C7—C8—C4	100.8 (1)	C8—C7—C6—C18	115.7 (1)
C1—C8—C4—C3	−22.7 (2)	C10—C12—C13—C14	−177.7 (1)
C1—C8—C4—C5	90.8 (1)	C10—C12—C17—C16	177.8 (1)
C1—C8—C4—C22	−147.5 (1)	C12—C13—C14—C15	−0.4 (2)
C1—C8—C7—C6	−112.6 (1)	C12—C17—C16—C15	0.2 (2)
C2—C1—C7—C6	3.8 (2)	C13—C12—C17—C16	−1.6 (2)
C2—C1—C7—C8	−94.3 (2)	C13—C14—C15—C16	−0.9 (2)
C2—C1—C8—C4	13.2 (2)	C14—C13—C12—C17	1.6 (2)
C2—C1—C8—C7	113.0 (1)	C14—C15—C16—C17	1.0 (2)

Symmetry codes: (i) $x-1, y, z$; (ii) $-x, y+1/2, -z+1/2$; (iii) $x+1/2, -y+1/2, -z$; (iv) $x-1/2, -y+1/2, -z$; (v) $-x+1, y-1/2, -z+1/2$.

A.9 X-ray crystal structure report for compound 200b



Sample: ban0908a

Compound: $C_{18}H_{20}O_3$

X-ray Structure Report

for

Christine Dietinger and Martin G. Banwell

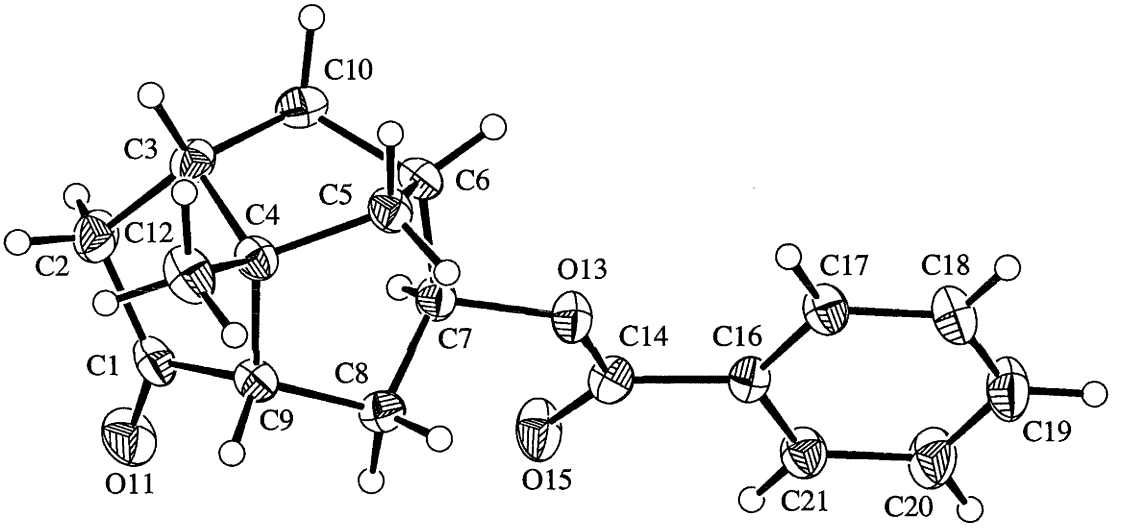
by

Anthony C. Willis

Research School of Chemistry,

The Australian National University, Canberra, ACT 0200, Australia

Wednesday, 22nd April, 2009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C3
C6
C5
C4
C12
C2
O13
C17
C18
C7
C14
C16
C1
C8
C9
C19
O11
O15
C21
C20

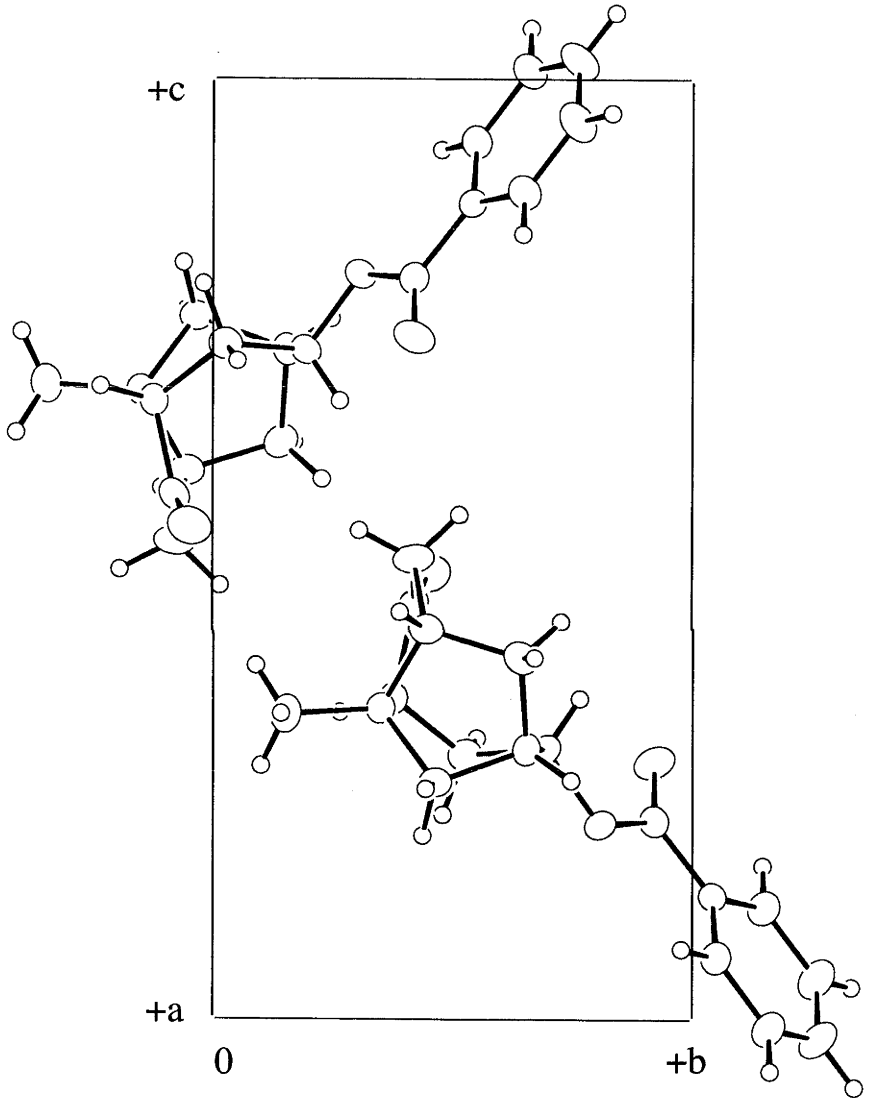
+c
+a
0
+b

Figure Captions for $C_{18}H_{20}O_3$

Figure 1. Molecular structure of $C_{18}H_{20}O_3$ with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

Figure 2. Unit cell packing diagram of $C_{18}H_{20}O_3$ projected down the *a* axis. Hydrogen atoms are drawn as circles with small radii.

Assignment of Chiral Centres

C3	S	C4	S	C6	S	C7	S
C9	S						

Calculated by PLATON.
Spek, A.L. (2001). PLATON - A Multipurpose Crystallographic Tool, Utrecht University, Utrecht, The Netherlands.

Crystal structure of $C_{18}H_{20}O_3$ — ban0908*a*

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Abstract

The crystal structure of $C_{18}H_{20}O_3$ is reported.

Comment

The compound is enantiometrically pure but the anomolous dispersion terms are very low for all elements in the structure and so the absolute configuration can not be determined in this experiment. Consequently Friedel-pair reflections have been averaged and the Flack parameter has not been refined. The absolute configuration of the molecule has been assigned on the basis of the synthetic precursors.

The crystallographic asymmetric unit consists of one molecule of $C_{18}H_{20}O_3$.

Experimental

The compound was prepared by CD and recrystallized from hexane/ethylacetate. The sample ID is CD-76.

Refinement

The H atoms were all located in a difference map, but were repositioned geometrically. The H atoms were initially refined with soft restraints on the bond lengths and angles to regularize their geometry (C—H in the range 0.93–0.98 Å) and with U_{iso}(H) in the range 1.2–1.5 times U_{eq} of the parent atom, after which the positions were refined with riding constraints.

The final difference electron density map is essentially featureless with the largest peaks lying outside the molecule or between H atoms of the methyl group.

Computing details

Data collection: *COLLECT* (Nonius, 1997-2001).; cell refinement: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *CRYSTALS* (Betteridge *et al.*, 2003); molecular graphics: *ORTEP*II (Johnson 1976) in *TEXSAN* (MSC, 1992-1997); software used to prepare material for publication: *CRYSTALS* (Betteridge *et al.*, 2003).

(ban0908a)

Crystal data

$C_{18}H_{20}O_3$	$V = 753.29\ (5)\ Å^3$
$M_r = 284.36$	$Z = 2$
Monoclinic, $P2_1$	Mo $K\alpha$
$a = 6.8933\ (3)$ Å	$\mu = 0.08\ mm^{-1}$
$b = 7.4523\ (2)$ Å	$T = 200$ K
$c = 14.8977\ (6)$ Å	0.35 × 0.10 × 0.04 mm
$\beta = 100.166\ (2)°$	

Data collection

Area diffractometer	1439 independent reflections
Absorption correction: integration via Gaussian method (Coppens, 1970) implemented in maXus (2000)	1084 reflections with $I > 2.0\sigma(I)$
$T_{min} = 0.983$, $T_{max} = 0.996$	$R_{int} = 0.073$
11449 measured reflections	

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.035$	H-atom parameters constrained
$wR(F^2) = 0.081$	$\Delta\rho_{max} = 0.18\ e\ Å^{-3}$
$S = 0.82$	$\Delta\rho_{min} = -0.25\ e\ Å^{-3}$
1439 reflections	Absolute structure: from synthesis
190 parameters	
1 restraint	

Table 1
Selected geometric parameters (Å, °)

C1—C2	1.488 (4)	C7—C8	1.518 (4)
C1—C9	1.524 (4)	C7—O13	1.472 (3)
C1—O11	1.216 (3)	C8—C9	1.530 (4)
C2—C3	1.533 (4)	O13—C14	1.347 (3)
C3—C4	1.551 (4)	C14—O15	1.211 (3)
C3—C10	1.541 (5)	C14—C16	1.477 (4)
C4—C5	1.525 (4)	C16—C17	1.398 (4)
C4—C9	1.567 (4)	C16—C21	1.377 (4)
C4—C12	1.525 (4)	C17—C18	1.377 (4)
C5—C6	1.528 (4)	C18—C19	1.368 (5)
C6—C7	1.533 (4)	C19—C20	1.381 (5)
C6—C10	1.538 (4)	C20—C21	1.376 (4)
C2—C1—C9	110.2 (2)	C8—C7—O13	109.1 (2)
C2—C1—O11	125.9 (3)	C7—C8—C9	111.1 (2)
C9—C1—O11	123.9 (3)	C8—C9—C1	110.6 (2)
C1—C2—C3	104.2 (2)	C8—C9—C4	113.6 (2)

C2—C3—C4	105.5 (2)	C1—C9—C4	105.3 (2)
C2—C3—C10	115.0 (3)	C3—C10—C6	106.5 (2)
C4—C3—C10	104.5 (2)	C7—O13—C14	117.5 (2)
C3—C4—C5	103.0 (2)	O13—C14—O15	123.0 (3)
C3—C4—C9	103.4 (2)	O13—C14—C16	112.6 (2)
C5—C4—C9	109.6 (2)	O15—C14—C16	124.4 (3)
C3—C4—C12	114.0 (3)	C14—C16—C17	121.9 (2)
C5—C4—C12	114.6 (3)	C14—C16—C21	119.4 (3)
C9—C4—C12	111.5 (2)	C17—C16—C21	118.8 (3)
C4—C5—C6	101.8 (2)	C16—C17—C18	120.2 (3)
C5—C6—C7	110.7 (2)	C17—C18—C19	120.1 (3)
C5—C6—C10	101.3 (2)	C18—C19—C20	120.4 (3)
C7—C6—C10	110.9 (2)	C19—C20—C21	119.6 (3)
C6—C7—C8	113.0 (2)	C16—C21—C20	120.9 (3)
C6—C7—O13	106.5 (2)		

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supplementary materials

Crystal structure of $C_{18}H_{20}O_3$ — ban0908*a*

Christine Dietinger, Martin G. Banwell and Anthony C. Willis

(ban0908a)

Crystal data

$C_{18}H_{20}O_3$	$F_{000} = 304$
$M_r = 284.36$	$D_x = 1.254$ Mg m^{-3}
Monoclinic, $P2_1$	Mo $K\alpha$ radiation $\lambda = 0.71073$ Å
$a = 6.8933$ (3) Å	Cell parameters from 7331 reflections
$b = 7.4523$ (2) Å	$\theta = 2.6$–$25°$
$c = 14.8977$ (6) Å	$\mu = 0.08$ mm^{-1}
$\beta = 100.166$ (2)°	$T = 200$ K
$V = 753.29$ (5) Å^3	Plate, colourless
$Z = 2$	0.35 × 0.10 × 0.04 mm

Data collection

Area diffractometer	1084 reflections with $I > 2.0\sigma(I)$
Monochromator: graphite	$R_{int} = 0.073$
$T = 200$ K	$\theta_{max} = 25.0°$
φ and ω scans with CCD	$\theta_{min} = 2.8°$
Absorption correction: integration via Gaussian method (Coppens, 1970) implemented in maXus (2000)	$h = -8 \rightarrow 8$
$T_{min} = 0.983$, $T_{max} = 0.996$	$k = -8 \rightarrow 8$
11449 measured reflections	$l = -17 \rightarrow 17$
1439 independent reflections	

Refinement

Refinement on F^2	Hydrogen site location: inferred from neighbouring sites
Least-squares matrix: full	H-atom parameters constrained
$R[F^2 > 2\sigma(F^2)] = 0.035$	Method = Modified Sheldrick $w = 1/[\sigma^2(F^2) + (0.04P)^2 + 0.0P]$, where $P = (\max(F_o^2,0) + 2F_c^2)/3$
$wR(F^2) = 0.081$	$(\Delta/\sigma)_{max} = 0.010$
$S = 0.82$	$\Delta\rho_{max} = 0.18$ e Å^{-3}
1439 reflections	$\Delta\rho_{min} = -0.25$ e Å^{-3}
190 parameters	Extinction correction: None
1 restraint	Absolute structure: from synthesis

Primary atom site location: structure-invariant direct methods

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters ($Å^2$)

	x	*y*	*z*	U_{iso}*/U_{eq}
C1	0.5114 (4)	0.4199 (4)	0.44157 (19)	0.0425
C2	0.7189 (4)	0.4206 (5)	0.49090 (19)	0.0514
C3	0.8415 (4)	0.4462 (4)	0.41548 (19)	0.0408
C4	0.7250 (4)	0.3500 (4)	0.3305 (2)	0.0369
C5	0.7690 (4)	0.4645 (4)	0.25165 (19)	0.0389
C6	0.7434 (4)	0.6542 (4)	0.28662 (19)	0.0366
C7	0.5253 (4)	0.6941 (4)	0.28691 (19)	0.0370
C8	0.3995 (4)	0.5260 (4)	0.2809 (2)	0.0417
C9	0.5046 (4)	0.3766 (4)	0.34107 (19)	0.0373
C10	0.8599 (4)	0.6419 (4)	0.3845 (2)	0.0431
O11	0.3663 (3)	0.4519 (4)	0.47490 (15)	0.0630
C12	0.7759 (5)	0.1517 (5)	0.3243 (2)	0.0535
O13	0.4568 (3)	0.8076 (3)	0.20670 (12)	0.0403
C14	0.3054 (4)	0.9199 (4)	0.21065 (19)	0.0398
O15	0.2143 (3)	0.9202 (3)	0.27311 (14)	0.0574
C16	0.2654 (4)	1.0416 (4)	0.13128 (19)	0.0360
C17	0.3893 (4)	1.0496 (4)	0.0665 (2)	0.0434
C18	0.3429 (5)	1.1593 (5)	−0.0085 (2)	0.0538
C19	0.1765 (6)	1.2628 (5)	−0.0195 (2)	0.0645
C20	0.0548 (5)	1.2593 (5)	0.0449 (2)	0.0618
C21	0.1001 (4)	1.1487 (4)	0.1196 (2)	0.0468
H21	0.7442	0.5152	0.5378	0.0620*
H22	0.7502	0.3060	0.5213	0.0614*
H31	0.9730	0.3922	0.4338	0.0484*
H51	0.9058	0.4445	0.2446	0.0476*
H52	0.6796	0.4379	0.1949	0.0478*
H61	0.7971	0.7472	0.2535	0.0456*
H71	0.5108	0.7651	0.3409	0.0441*
H81	0.2712	0.5505	0.2987	0.0506*
H82	0.3780	0.4799	0.2171	0.0505*
H91	0.4269	0.2648	0.3264	0.0440*
H101	0.9989	0.6700	0.3843	0.0509*
H102	0.8125	0.7280	0.4241	0.0513*
H121	0.6997	0.0995	0.2691	0.0827*
H122	0.9185	0.1412	0.3248	0.0826*
H123	0.7478	0.0887	0.3761	0.0823*
H171	0.5064	0.9770	0.0750	0.0524*
H181	0.4270	1.1621	−0.0535	0.0669*
H191	0.1433	1.3381	−0.0700	0.0778*
H201	−0.0593	1.3313	0.0359	0.0738*
H211	0.0180	1.1460	0.1640	0.0566*

Atomic displacement parameters ($Å^2$)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
C1	0.0493 (18)	0.0391 (17)	0.0439 (17)	0.0046 (16)	0.0211 (14)	0.0090 (16)
C2	0.0486 (18)	0.073 (2)	0.0339 (16)	0.0064 (19)	0.0117 (14)	0.0050 (18)
C3	0.0329 (15)	0.0516 (18)	0.0380 (15)	0.0097 (16)	0.0065 (12)	0.0017 (17)
C4	0.0381 (16)	0.0348 (17)	0.0399 (17)	0.0023 (13)	0.0123 (13)	0.0016 (13)
C5	0.0390 (16)	0.0449 (18)	0.0355 (15)	0.0017 (14)	0.0139 (12)	0.0000 (14)
C6	0.0354 (16)	0.0324 (16)	0.0442 (18)	−0.0016 (14)	0.0130 (13)	0.0022 (14)
C7	0.0378 (16)	0.0382 (18)	0.0355 (17)	0.0043 (13)	0.0074 (13)	0.0054 (14)
C8	0.0339 (15)	0.0481 (19)	0.0422 (19)	−0.0001 (14)	0.0045 (13)	0.0016 (15)
C9	0.0368 (15)	0.0337 (15)	0.0429 (17)	−0.0003 (13)	0.0114 (13)	0.0017 (14)
C10	0.0330 (15)	0.0491 (18)	0.0467 (17)	0.0004 (16)	0.0057 (13)	−0.0080 (17)
O11	0.0557 (13)	0.0814 (18)	0.0605 (15)	0.0114 (14)	0.0341 (11)	0.0086 (15)
C12	0.064 (2)	0.0396 (18)	0.063 (2)	0.0080 (18)	0.0277 (17)	0.0043 (18)
O13	0.0476 (11)	0.0400 (11)	0.0353 (11)	0.0112 (10)	0.0125 (9)	0.0059 (10)
C14	0.0418 (16)	0.0362 (16)	0.0409 (17)	0.0064 (16)	0.0065 (13)	−0.0016 (15)
O15	0.0606 (13)	0.0723 (16)	0.0457 (13)	0.0269 (14)	0.0273 (11)	0.0149 (13)
C16	0.0429 (16)	0.0318 (15)	0.0325 (16)	0.0019 (14)	0.0043 (13)	−0.0019 (13)
C17	0.0501 (17)	0.0373 (16)	0.0451 (18)	0.0053 (16)	0.0144 (15)	0.0026 (15)
C18	0.069 (2)	0.046 (2)	0.051 (2)	0.0033 (19)	0.0223 (16)	0.0112 (18)
C19	0.078 (2)	0.061 (2)	0.056 (2)	0.012 (2)	0.0139 (19)	0.025 (2)
C20	0.062 (2)	0.057 (2)	0.066 (2)	0.0215 (19)	0.0112 (18)	0.020 (2)
C21	0.0484 (18)	0.0445 (18)	0.0488 (19)	0.0071 (18)	0.0124 (15)	0.0059 (18)

Geometric parameters (Å, °)

C1—C2	1.488 (4)	C8—H81	0.984
C1—C9	1.524 (4)	C8—H82	0.997
C1—O11	1.216 (3)	C9—H91	0.993
C2—C3	1.533 (4)	C10—H101	0.982
C2—H21	0.986	C10—H102	0.966
C2—H22	0.973	C12—H121	0.975
C3—C4	1.551 (4)	C12—H122	0.985
C3—C10	1.541 (5)	C12—H123	0.953
C3—H31	0.985	O13—C14	1.347 (3)
C4—C5	1.525 (4)	C14—O15	1.211 (3)
C4—C9	1.567 (4)	C14—C16	1.477 (4)
C4—C12	1.525 (4)	C16—C17	1.398 (4)
C5—C6	1.528 (4)	C16—C21	1.377 (4)
C5—H51	0.978	C17—C18	1.377 (4)
C5—H52	0.974	C17—H171	0.961
C6—C7	1.533 (4)	C18—C19	1.368 (5)
C6—C10	1.538 (4)	C18—H181	0.960
C6—H61	0.961	C19—C20	1.381 (5)
C7—C8	1.518 (4)	C19—H191	0.934
C7—O13	1.472 (3)	C20—C21	1.376 (4)
C7—H71	0.982	C20—H201	0.942

C8—C9	1.530 (4)	C21—H211	0.944
O11···C3^{i}	3.570 (3)	O15···C2^{ii}	3.464 (4)
O11···C2^{ii}	3.593 (5)		
C2—C1—C9	110.2 (2)	C9—C8—H82	106.5
C2—C1—O11	125.9 (3)	H81—C8—H82	109.4
C9—C1—O11	123.9 (3)	C8—C9—C1	110.6 (2)
C1—C2—C3	104.2 (2)	C8—C9—C4	113.6 (2)
C1—C2—H21	112.8	C1—C9—C4	105.3 (2)
C3—C2—H21	112.2	C8—C9—H91	107.5
C1—C2—H22	109.9	C1—C9—H91	108.3
C3—C2—H22	110.2	C4—C9—H91	111.5
H21—C2—H22	107.5	C3—C10—C6	106.5 (2)
C2—C3—C4	105.5 (2)	C3—C10—H101	109.6
C2—C3—C10	115.0 (3)	C6—C10—H101	109.3
C4—C3—C10	104.5 (2)	C3—C10—H102	113.0
C2—C3—H31	110.2	C6—C10—H102	111.3
C4—C3—H31	110.8	H101—C10—H102	107.2
C10—C3—H31	110.5	C4—C12—H121	110.0
C3—C4—C5	103.0 (2)	C4—C12—H122	108.5
C3—C4—C9	103.4 (2)	H121—C12—H122	111.3
C5—C4—C9	109.6 (2)	C4—C12—H123	110.3
C3—C4—C12	114.0 (3)	H121—C12—H123	109.3
C5—C4—C12	114.6 (3)	H122—C12—H123	107.5
C9—C4—C12	111.5 (2)	C7—O13—C14	117.5 (2)
C4—C5—C6	101.8 (2)	O13—C14—O15	123.0 (3)
C4—C5—H51	108.9	O13—C14—C16	112.6 (2)
C6—C5—H51	110.4	O15—C14—C16	124.4 (3)
C4—C5—H52	111.9	C14—C16—C17	121.9 (2)
C6—C5—H52	113.0	C14—C16—C21	119.4 (3)
H51—C5—H52	110.5	C17—C16—C21	118.8 (3)
C5—C6—C7	110.7 (2)	C16—C17—C18	120.2 (3)
C5—C6—C10	101.3 (2)	C16—C17—H171	119.1
C7—C6—C10	110.9 (2)	C18—C17—H171	120.7
C5—C6—H61	114.5	C17—C18—C19	120.1 (3)
C7—C6—H61	109.1	C17—C18—H181	119.8
C10—C6—H61	110.2	C19—C18—H181	120.1
C6—C7—C8	113.0 (2)	C18—C19—C20	120.4 (3)
C6—C7—O13	106.5 (2)	C18—C19—H191	121.1
C8—C7—O13	109.1 (2)	C20—C19—H191	118.5
C6—C7—H71	110.4	C19—C20—C21	119.6 (3)
C8—C7—H71	110.7	C19—C20—H201	119.0
O13—C7—H71	106.9	C21—C20—H201	121.4
C7—C8—C9	111.1 (2)	C16—C21—C20	120.9 (3)
C7—C8—H81	111.2	C16—C21—H211	119.0
C9—C8—H81	109.4	C20—C21—H211	120.1
C7—C8—H82	109.2		
O11—C1—C2—C3	−158.5 (3)	C3—C10—C6—C7	86.7 (3)
O11—C1—C9—C4	178.8 (3)	C4—C3—C10—C6	3.7 (3)

O11—C1—C9—C8	55.7 (4)	C4—C5—C6—C7	−71.3 (3)
O13—C7—C6—C5	−102.5 (3)	C4—C5—C6—C10	46.4 (3)
O13—C7—C6—C10	145.9 (2)	C4—C9—C8—C7	−46.6 (3)
O13—C7—C8—C9	159.8 (2)	C5—C4—C3—C10	25.0 (3)
O13—C14—C16—C17	−7.1 (4)	C5—C4—C9—C8	−8.1 (3)
O13—C14—C16—C21	171.9 (2)	C5—C6—C7—C8	17.3 (3)
O15—C14—O13—C7	−6.4 (4)	C6—C5—C4—C9	64.8 (3)
O15—C14—C16—C17	172.5 (3)	C6—C5—C4—C12	−169.0 (2)
O15—C14—C16—C21	−8.5 (4)	C6—C7—O13—C14	−152.9 (2)
C1—C2—C3—C4	−32.9 (3)	C6—C7—C8—C9	41.5 (3)
C1—C2—C3—C10	81.8 (3)	C7—O13—C14—C16	173.2 (2)
C1—C9—C4—C3	−19.9 (3)	C8—C7—O13—C14	84.9 (3)
C1—C9—C4—C5	−129.2 (2)	C8—C7—C6—C10	−94.3 (3)
C1—C9—C4—C12	102.9 (3)	C8—C9—C4—C12	−136.0 (3)
C1—C9—C8—C7	71.5 (3)	C9—C4—C3—C10	−89.1 (3)
C2—C1—C9—C4	−0.1 (3)	C10—C3—C4—C12	149.8 (3)
C2—C1—C9—C8	−123.1 (3)	C14—C16—C17—C18	177.3 (3)
C2—C3—C4—C5	146.7 (2)	C14—C16—C21—C20	−177.9 (3)
C2—C3—C4—C9	32.6 (3)	C16—C17—C18—C19	0.8 (5)
C2—C3—C4—C12	−88.5 (3)	C16—C21—C20—C19	0.2 (5)
C2—C3—C10—C6	−111.6 (3)	C17—C16—C21—C20	1.2 (4)
C3—C2—C1—C9	20.3 (3)	C17—C18—C19—C20	0.6 (5)
C3—C4—C5—C6	−44.7 (3)	C18—C17—C16—C21	−1.7 (4)
C3—C4—C9—C8	101.2 (3)	C18—C19—C20—C21	−1.1 (5)
C3—C10—C6—C5	−30.7 (3)		

Symmetry codes: (i) $x-1, y, z$; (ii) +1, , +1.

Appendix B

Publication resulting from research undertaken during PhD candidature

Tetrahedron
journal homepage: www.elsevier.com

Chemoenzymatic and enantioselective assembly of the (1α,3aβ,6α,7aβ)-octahydro-1,6-methano-1*H*-indene framework associated with 2-isocyanoallopupukeanane: validation of a new synthetic strategy and the identification of enantiomeric switching regimes

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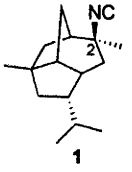
ABSTRACT

The octahydro-1,6-methano-1*H*-indene framework associated with the marine sesquiterpenoid 2-isocyanoallopupukeanane (**1**) has been prepared in enantiomerically pure form from the *cis*-1,2-dihydrocatechol **5** using Diels–Alder cycloaddition, oxa-di-π-methane rearrangement and intramolecular enolate alkylation steps as the key bond-forming events. Three distinct strategies for employing such sequences in the selective synthesis of either enantiomeric form of the target framework have been identified.

1. Introduction

In 1991 Fusetani et al. reported[1] on the elucidation, using 2D NMR spectroscopic techniques, of the structure of 2-isocyanoallopupukeanane (**1**), a sesquiterpenoid isonitrile isolated from two specimens of a *Phyllidia pustulosa* species of nudibranch collected off Hachijo-jima Island, Japan. Such isocyano-containing species, which include the framework-isomeric natural products 2-isocyanopupukeanane,[2] 9-isocyanopupukeanane[2] and 9-isocyanoneopupukeanane,[3] are found in the secretions of a variety of marine molluscs, where they are presumed to play a defensive role, and are known to be sequestered from the sponge diet of these creatures.[2c] The origins of the isocyano-function have been the subject of various studies[4,5] including a number conducted by one of us (MJG).[5]



1

As part of a program directed towards developing a comprehensive understanding of the biogenesis of compound **1** we sought to establish methods for synthesizing, in either enantiomeric form,[6] the associated octahydro-1,6-methano-1*H*-indene framework incorporating relevant functionality, especially those that would allow for ready installation of isocyano and related groups at the 2-position. In contrast to the situation with 2-isocyanopupukeanane and 9-isocyano-pupukeanane,[7] there have been few studies concerned with the total synthesis of 2-isocyanoallopupukeanane (**1**) or its enantiomer.[8,9] Indeed, the single reported total synthesis of the title natural product was described by Ho and co-workers in 1999[8] and only provided the racemic modification of the target. More recently (2006), Srikrishna and Satyanarayana have communicated[9] a biogenetically patterned and enantiospecific synthesis of "allopupukeanones" from 6-methylcarvone that involves, as the key step, the acid-induced Wagner–Meerwein rearrangement of a pupukeanyl cation to the corresponding allopupukeanane species. However, the extension of such chemistry to the preparation of natural product **1** has not been reported thus far.

The approach to the tricyclic framework of *ent*-2-isocyanoallopupukeanane (*ent*-**1**) that we have pursued is outlined in Fig. 1 and this incorporates several key transformations used during the course of our development of total syntheses of various triquinane-type sesquiterpenes including hirsutene, hirsutic acid, complicatic acid and phellodonic acid.[10] A pivotal aspect of the present work was the recognition that the framework of target *ent*-**1** (and **1**) is a

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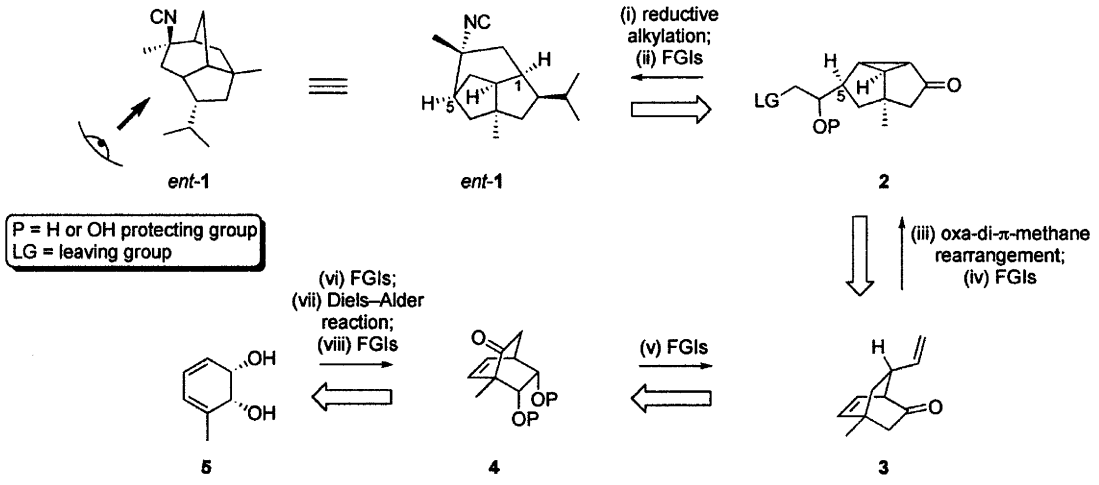


Figure 1. Retrosynthetic analysis of *ent*-2-isocyanoallopupukeanane (*ent*-**1**).

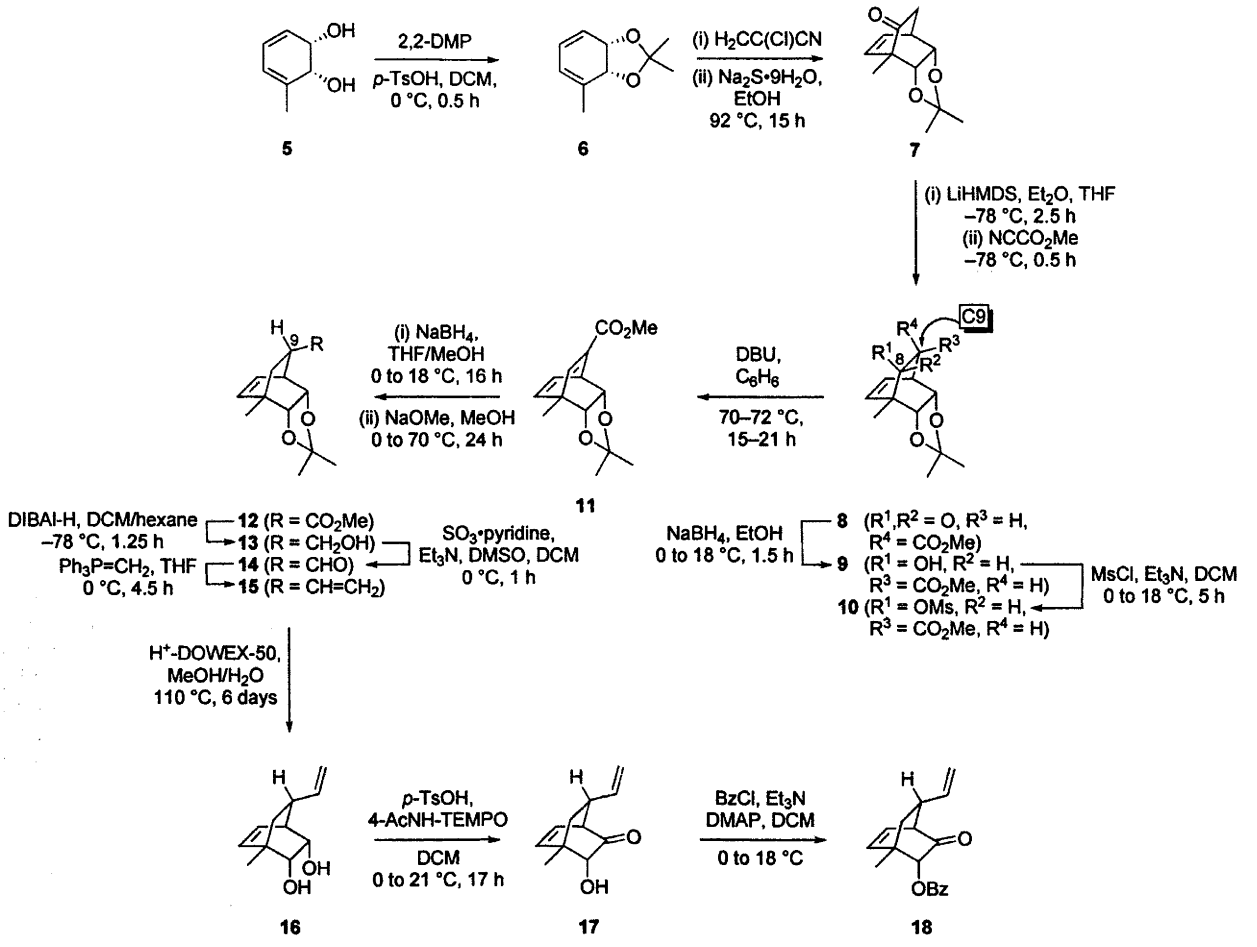
1,5-ethano-bridged diquinane and that this could, therefore, be assembled from a precursor of the general form **2** through its subjection to reductive cleavage of the carbonyl-conjugated cyclopropane moiety and in situ intramolecular alkylation of the ensuing enolate by the C5-appended and *endo*-orientated side-chain bearing a leaving group at its terminus. Conventional functional group interconversions (FGIs) of the OP and carbonyl groups within the anticipated product of this sequence should then deliver *ent*-2-isocyanoallopupukeanane (*ent*-**1**) and related compounds. It was expected that compound **2** could, in turn, be obtained via a photochemically-promoted oxa-di-π-methane rearrangement[11] of the disubstituted bicyclo[2.2.2]octenone **3** followed by or, if necessary, preceded by manipulation of the associated vinyl group so as to establish the relevant functionality on the side-chain of compound **2**. Access to compound **3** was expected to be gained via conventional manipulations of ketone **4**, versions of which we have obtained previously through Diels–Alder cycloaddition reactions between α-chloroacrylonitrile and hydroxy-protected forms of the *cis*-1,2-dihydrocatechol **5**.[12] Starting material **5** is readily obtained in multi-gram quantities and enantiomerically pure form (>99.8% ee) through the whole-cell biotransformation of toluene using a genetically engineered micro-organism *E. coli* JM109 (pDTG601) that over-expresses the responsible enzyme, viz. toluene-dioxygenase (TDO).[13] In an overall sense, then, there are three critical chemical sequences associated with the implementation of the proposed synthetic plan, namely the Diels–Alder cycloaddition process leading to compounds of the general form **4** and the manipulation of such adducts to give bicyclo[2.2.2]octenone **3**, the photochemical rearrangement of the latter to give, after appropriate FGIs, the cyclopropa-fused diquinane **2** and, finally, a reductive alkylation process leading to the complete tricyclic framework associated with target *ent*-**1**. Each of these pivotal steps is discussed separately in the following sections as is the capacity to adapt the reported chemistry to the synthesis of either enantiomeric form of 2-isocyanoallopupukeanane, viz. **1** and/or *ent*-**1**.

2. Results and discussion

2.1. Synthesis of the substrate for the oxa-di-π-methane rearrangement reaction

The first critical chemical sequence associated with the present work started (Scheme 1) with the engagement of the well known[14] acetonide derivative, **6**, of *cis*-1,2-dihydrocatechol **5** in a Diels–Alder cycloaddition reaction with α-chloroacrylonitrile. Hydrolysis of the ensuing mixture of epimeric α-chloronitriles[12] to give the previously reported ketone **7**[12] was achieved most effectively using a modification of conditions originally reported by Evans et al.[15] As a prelude to introducing the vinyl group required in a photochemical substrate of the general form **3**, the enolate anion derived by deprotonation of ketone **7** was treated, in diethyl ether, with two molar equivalents of Mander's reagent[16] and thus affording the β-keto ester **8** in 67% yield. Reduction of the latter with sodium borohydride in ethanol then gave β-hydroxyester **9** and its stereoisomers C9-*epi*-**9** and C8,C9-di-*epi*-**9** in 82% combined yield.[17] The structure of compound **9** was confirmed by single-crystal X-ray analysis (see Experimental section).

Compound C9-*epi*-**9**, the predominant product of the reduction process, could be converted into isomer **9** (67% yield at 73% conversion) upon treatment with the weakly nucleophilic base DBU. Subjection of a mixture of compounds **9** and C8,C9-di-*epi*-**9** to mesylation under the Crossland–Servis conditions[18] then gave the corresponding mixture of mesylate **10** and isomer C8,C9-di-*epi*-**10**. Treatment of the latter mixture with DBU in hot (70–72 °C) benzene overnight resulted in elimination of the elements of methanesulfonic acid and formation of the unsaturated ester **11** (92%). Reaction of compound **11** with sodium borohydride in methanol/THF then gave a ca. 1:1 mixture of ester **12** and its epimer C9-*epi*-**12** (81% combined yield) that could be separated from one another by conventional flash chromatographic techniques. Interestingly, treatment of compound C9-*epi*-**12** with sodium methoxide in methanol at 0 to 70 °C for 24 h afforded a ca. 3:1 mixture of the starting material and epimer **12** (89% combined yield) and thus demonstrating that additional quantities of the desired isomer (**12**) could be generated from the unwanted one. Treatment of ester **12** with DIBAL-H in dichloromethane/hexane at –78 °C for 1.25 h afforded a chromatographically separable mixture of alcohol **13** (57%) and aldehyde **14** (30%). The former product could be oxidised to the latter in 51% yield using the Parikh–Doering protocol.[19] Additional quantities of aldehyde **14** could also be obtained by reducing ester C9-*epi*-**12** to aldehyde C9-*epi*-**14** and then epimerising the latter with DBU (47% yield of compound **14** over the two steps). Wittig-type methylenation of aldehyde **14** then gave the required olefin **15** in 60% yield. Cleavage of the acetonide unit within the latter compound was achieved by exposing the substrate to activated DOWEX-50 resin in refluxing aqueous methanol for six days. By this means the diol **16** was



Scheme 1.

obtained in 66% yield. So, despite the harsh conditions required to effect cleavage of the acetonide group, there appeared to be no complications arising from isomerisation of the terminal olefin into a more stable internal position. Selective oxidation of the hydroxyl group remote from the bridgehead methyl group within diol **16** could be achieved using the sterically demanding oxammonium salt derived from reaction of 4-AcNH-TEMPO with *p*-TsOH•H_2O[20] and the ensuing acyloin **17** (81%) was immediately subjected to *O*-benzoylation using benzoyl chloride in the presence of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) and triethylamine. By such means the keto-ester **18** was obtained in quantitative yield.

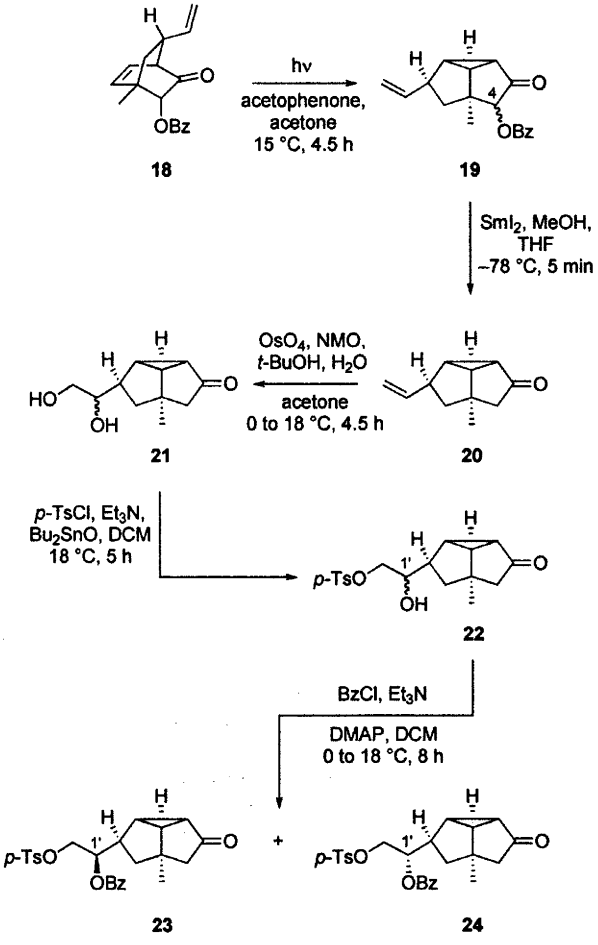
While in the original plan (Fig. 1) deletion of the *O*-benzoyl group within keto-ester **18** would now be required in order to produce the photo-substrate **3**, our previous studies[10] had shown that systems related to the former compound readily engage in oxa-di-π-methane rearrangement reactions. Accordingly, and given the capacity to delete the OBz group at a later stage in the synthesis, compound **18** was selected as the substrate to be used in studies of the photochemical rearrangement process. Details are presented in the following section.

2.2. The oxa-di-π-methane rearrangement reaction and chemical manipulation of the photoproduct

Following procedures developed earlier,[10] a solution of compound **18** in acetone containing acetophenone (triplet sensitiser) was subjected to irradiation with a medium pressure mercury-vapour lamp at 15 °C for 4.5 h (Scheme 2). By such means a ca. 1:1 mixture of the C4-epimeric forms of compound **19** was obtained, albeit in a disappointing 32% combined yield. This low yield could be attributed to interference from the vinyl group associated with substrate **18**, especially the potential for this moiety to participate in a competing oxa-di-π-methane rearrangement process. The formation of the C4-epimeric forms of product **19** from a single epimeric form of precursor **18** presumably arises from a secondary photochemical process involving photo-enolisation and/or Norrish-type 1 reactions[10] of the primary photo-product. The driving force for the epimerisation of the primary photo-product is the migration of the *O*-benzoyl unit from the *exo*-face to the *endo*-face of the cyclopropa-fused diquinane framework so as to relieve steric interactions with the adjacent methyl group.

The chemical manipulation of photo-product **19** so as to generate a substrate for examination of the proposed intramolecular enolate alkylation step (Fig. 1) involved initial reductive removal of the *O*-benzoyl residue. This was best accomplished by treating a methanolic solution of compound **19** with 2.2 molar equivalents of samarium iodide at –78 °C for 5 minutes.[21] The ensuing unsaturated ketone **20** (54%) was subjected to olefin dihydroxylation using the UpJohn conditions[22] and thereby affording an inseparable and 1:1 mixture of the diastereoisomeric forms of the product diol **21** in 48% combined yield. Attempts to improve upon this outcome, in terms of both yield and diastereoselectivity, by using Sharpless asymmetric dihydroxylation protocols[23] either gave no reaction at all (with AD-mix-β) or resulted in a 1:1:1 mixture of the starting material and the product diols (with AD-mix-α). The selective tosylation

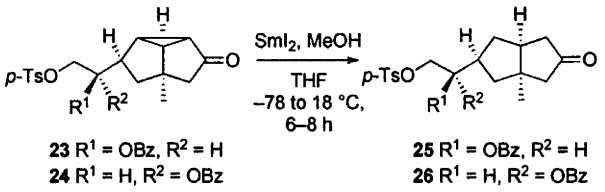
of the primary hydroxy group within compound **21** was readily accomplished using *p*-toluenesulfonyl chloride in the presence of dibutyltin oxide[24] and thereby affording the desired epimeric mono-tosylates **22** in 77% combined yield. *O*-Benzoylation of the secondary hydroxyl groups within the epimeric forms of compound **22** was effected under standard conditions (BzCl, DMAP, Et_3N) and the co-formed bis-esters **23** and **24** were readily separated from one another by conventional chromatographic techniques and thereby obtained in yields of 40% and 55%, respectively. The illustrated stereochemistries assigned to products **23** and **24** follow from a single-crystal X-ray analysis of a derivative of the former compound (vide infra).



Scheme 2.

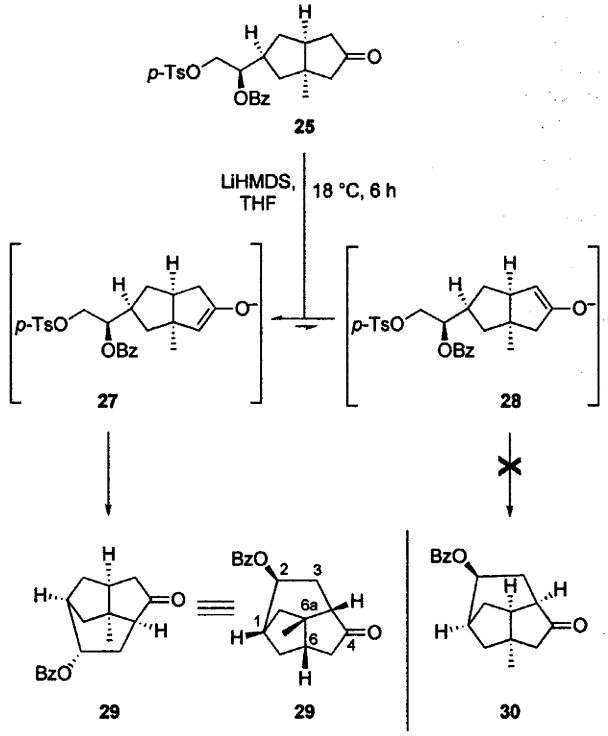
2.3. Completion of the synthesis through intramolecular enolate alkylation

With compounds **23** and **24** in hand studies of the validity of the proposed reductive-cleavage/intramolecular enolate alkylation chemistry (see conversion **2** → **1**, Fig. 1) could begin. The initial experiments simply involved treating each of substrates **23** and **24** with 1.2 molar equivalents of samarium diiodide in THF/methanol at –78 to 18 °C for periods of up to fourteen hours (Scheme 3).[25] However, after quenching the reaction mixtures and then subjecting them to work up, only the products of cyclopropane ring-cleavage, viz. compounds **25** and **26**, were obtained in yields of 52% and 21%, respectively. The lack of any products of intramolecular enolate alkylation processes may be attributed to the limited nucleophilicity and/or the ready protonation of the intermediate samarium enolate.[25,26]



Scheme 3.

Sufficient quantities of compound **25** were obtained by the means just described to allow for an investigation of the intramolecular enolate alkylation reaction under more conventional conditions. Thus, treatment of a THF solution of ketone **25** maintained at –78 °C with 1.2 molar equivalents of lithium hexamethyldisilazide (LiHMDS) (Scheme 4) and then allowing the reaction mixture to warm to 18 °C provided, after work up and chromatographic purification, compound **29** in 50% yield. All the spectroscopic data obtained on this material were in full accord with the assigned structure but final confirmation of this was secured by a single-crystal X-ray analysis. The derived ORTEP is shown in Fig. 2 while other details of this analysis are presented in the experimental section. The formation of this product must arise through selective formation of precursor enolate **27** which then engages in intramolecular alkylation with the tosyloxy-bearing side chain to give ketone **29** incorporating the tricyclic framework of 2-isocyanoallopupukeanane but carrying the methyl group in the C6a rather than the desired C6 position. Interestingly, no evidence could be obtained for the formation of the isomeric ketone **30** that would arise from intramolecular alkylation of intermediate **28**.



Scheme 4.

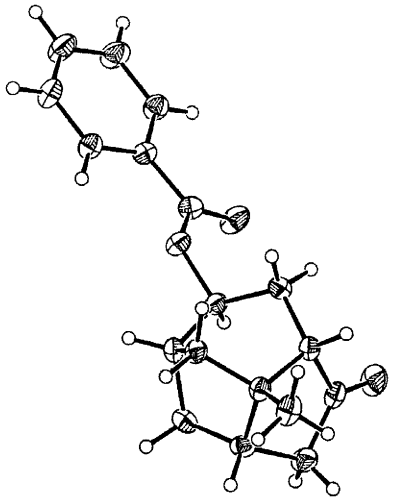


Figure 2. Molecular structure of compound **29** ($C_{18}H_{20}O_3$). Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

Presumably, the selective formation of enolate **27** over isomer **28** under the conditions of thermodynamic control[27] defined above is a reflection of the greater reduction in torsional strain (between the angular methyl and the *syn*-1,2-related methylene proton adjacent to the carbonyl group) associated with the conversion **25** → **27** than would be encountered in the equivalent process leading to **28** (where the corresponding reduction in torsional strain would "only" be that arising from loss of the interaction between the angular hydrogen and the *syn*-1,2-related methylene proton adjacent to the carbonyl group). In principle, carrying out enolate formation under conditions of kinetic control (viz. adding the substrate ketone **25** to a solution of the base)[27] might be expected to lead to enolate **28** and thence the tricyclic product **30** which bears a pseudo-enantiomeric relationship to isomer **29**. Unfortunately, a lack of sufficient quantities of ketone **25** has prevented us from conducting the relevant experiments. Current efforts are directed towards achieving a much more efficient route to compound **25** and the results of these will be reported in due course.

2.4. Potentially enantiodivergent routes to the octahydro-1,6-methano-1H-indene framework associated with 2-isocyanoallopupukeanane

The lack of certainty regarding the absolute configuration of the naturally-occurring form of 2-isocyanoallopupukeanane[6] has prompted us to consider ways in which either enantiomeric form of this compound could be synthesised using the now validated strategy shown in Fig. 1. Three distinct ways of achieving this seem possible. First of all, the enantiomeric form of the starting material, viz. compound *ent*-**5**, is available from *p*-iodotoluene using methodology reported by Boyd and co-workers.[28] Accordingly, the optical antipodes of all of compounds **6**–**26** and **29** are automatically available using the chemistries reported herein. Another possible mode of entry into the other enantiomeric series would involve reversing the facial selectively of the initial Diels–Alder cycloaddition reaction involving *cis*-1,2-dihydrocatechol **5** and/or its derivatives since an α-face addition process affords the pseudo-enantiomeric form of the compound (e.g. ketone **7**) arising from the corresponding β-face addition reaction. In recent work[10a,10b,29] we have shown that such facial selectivities can be controlled, to some extent at least, by using either compound **5** or a protected form thereof (e.g. acetonide **6**) as the 4π-addend in the cycloaddition process. A third possible mode of enantiomeric "switching" arises from the pseudo-symmetrical nature of ketonic systems such as compound **25**. In particular, if the non-methylated variant of this diquinane could be obtained from the known, benzene-derived *cis*-1,2-dihydrocatechol[13] then this could be desymmetrised using the relevant Koga–Simpkins type-base[30] to generate either enantiomeric form of the corresponding enolate and thence, through intramolecular alkylation, either enantiomeric form of the title framework.[31] The required methyl group could then be introduced through a conventional dehydrogenation/conjugate addition reaction sequence. Efforts to examine all of these possibilities are now underway in our laboratories. Results will be reported in due course.

3. Experimental section

3.1. General experimental procedures

Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on a Varian Gemini machine operating at 300 or 75 MHz, respectively. Unless otherwise specified, spectra were acquired at 20 °C in deuterochloroform ($CDCl_3$) that had been stored over anhydrous sodium carbonate. Chemical shifts are recorded as δ values in parts per million (ppm). Infrared spectra (ν_{max}) were normally recorded on a Perkin–Elmer 1800 Series FTIR Spectrometer and samples were analysed as thin films on KBr plates (for liquids) or as a KBr disk (for solids). Low-resolution ESI mass spectra were recorded in positive-ion mode on a Micromass–Waters LC-ZMD single quadrupole liquid chromatograph-mass spectrometer while low- and high-resolution EI mass spectra were recorded on a Fisons VG AUTOSPEC instrument. Melting points were measured on a Stanford Research Systems Optimelt-Automated Melting Point System and are uncorrected. Optical rotations were measured at the sodium-D line (λ = 589 nm) between 17 and 20 °C and at the concentrations (*c*, in g/100 mL) indicated using spectroscopic grade chloroform ($CHCl_3$) as solvent. Analytical thin layer chromatography (TLC) was performed on aluminium-backed 0.2 mm thick silica gel 60 F254 plates as supplied by Merck. Eluted plates were visualised using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included a mixture of vanillin : sulfuric acid : ethanol (1 g : 1 g : 18 mL) or phosphomolybdic acid : ceric sulfate : sulfuric acid (conc.) : water (37.5 g : 7.5 g : 37.5 g : 720 mL). The retardation factor (R_f) values cited here have been rounded to the first decimal point. Flash chromatographic separations were carried out following protocols defined by Still et al.[32] with silica gel 60 (0.040–0.0063 mm) as the stationary phase and using the AR- or HPLC-grade solvents indicated. Starting materials and reagents were generally available from the Sigma–Aldrich, Merck, TCI, Strem or Lancaster Chemical Companies and were either used as supplied or, in the case of liquids, distilled when required. Drying agents and other inorganic salts were purchased from the AJAX, BDH or Unilab Chemical Companies. THF, dichloromethane, acetonitrile and benzene were dried using a Glass Contour solvent purification system that is based upon a technology originally described by Grubbs et al.[33] Spectroscopic grade solvents were used for all analyses. Where necessary, reactions were performed under a nitrogen or argon atmosphere.

3.2. Specific chemical transformations

3.2.1. Compound 8

LiHMDS (28.8 mL of a 1 M solution in THF, 28.8 mmol, 2 molar equiv.) was diluted with diethyl ether (132 mL) then cooled to –78 °C. A solution of ketone **7** (3.00 g, 14.40 mmol) in diethyl ether (12 mL) was then added to the reaction mixture via

syringe pump at the rate of 15 mL/h. After addition was complete, the resulting mixture was stirred at –78 °C for 2.5 h then methyl cyanoformate (Mander's reagent) (2.45 g or 2.30 mL, 28.8 mmol, 2 molar equiv.) was added via syringe pump at 0.45 mL/h. The ensuing mixture was stirred at –78 °C for 0.5 h after which it was poured into dichloromethane/water (300 mL of a 1:1 v/v mixture). The separated aqueous phase was extracted with dichloromethane (3 × 100 mL) and the combined organic layers were washed with brine (1 × 150 mL) then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The orange oil thus obtained was subjected to column chromatography (silica, 1:4 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.2) gave *β-ketoester* ***8*** (2.56 g, 67%) as a white, crystalline solid. This material was used in the subsequent steps of the synthesis (see below). For the purposes of analysis a sample of this material was recrystallised (ethyl acetate/hexane) to give colourless crystals, mp = 115–116°C, $[\alpha]_D$ = +210.0 (*c* 1, $CHCl_3$) (Found: $M^{+\bullet}$, 266.1163; C, 63.43, H, 6.91. $C_{14}H_{18}O_5$ requires $M^{+\bullet}$, 266.1154; C, 63.15, H, 6.81%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.44 (broad dd, J = 8.1 and 6.4 Hz, 1H), 5.71 (broad dt, J = 8.1 and 1.5 Hz, 1H), 4.49 (broad dd, J = 7.1 and 3.4 Hz, 1H), 4.08 (dd, J = 7.1 and 1.5 Hz, 1H), 3.71 (s, 3H), 3.46–3.41 (complex m, 1H), 2.92 (d, J = 1.6 Hz, 1H), 1.37 (s, 3H), 1.35 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 202.0 (C), 167.8 (C), 133.0 (CH), 129.2 (CH), 110.9 (C), 79.4 (CH), 78.1 (CH), 54.6 (C), 52.8 (CH_3), 50.4 (CH), 38.3 (CH), 25.3 (CH_3), 25.0 (CH_3), 14.6 (CH_3); IR ν_{max} (KBr) 2979, 2949, 2937, 2891, 1747, 1725, 1374, 1262, 1243, 1207, 1163, 1088, 1063, 1034, 973, 714 cm^{-1}; MS (EI, 70 eV) *m/z* 266 ($M^{+\bullet}$, 48%), 251 [$(M–CH_3\cdot)^+$, 45], 235 (24), 176 (100), 148 (93), 121 (71), 108 (69), 100 (89), 91 (63), 85 (65), 43 (68).

3.2.2. Compound 9

Method A: A solution of *β*-ketoester **8** (101 mg, 380 μmol) in ethanol (17.4 mL) was cooled to 0°C then treated, in one portion, with sodium borohydride (14.4 mg, 380 μmol, 1 molar equiv.). The ensuing mixture was stirred at 0 °C for 0.5 h then allowed to warm to 18 °C. After 1 h at this temperature the reaction mixture was treated with ammonium chloride (5 mL of a saturated aqueous solution) and, after a further 0.08 h, with distilled water (50 mL) then concentrated under reduced pressure to ca. 1/3 of its original volume. The residue so obtained was diluted with dichloromethane (10 mL). The separated aqueous phase was extracted with dichloromethane (3 × 10 mL) and the combined organic phases were then washed with brine (1 × 10 mL) before being dried (magnesium sulfate), filtered and concentrated under reduced pressure. The resulting yellow oil was subjected to column chromatography (silica, 1:7:12 v/v/v MeOH/ethyl acetate/hexane elution) to afford two fractions, A and B.

Concentration of fraction A (R_f = 0.4 in 1:7:12 v/v/v MeOH/ethyl acetate/hexane) yielded an inseparable 1:1.7 mixture of *compounds* ***9*** and *C8,C9-di*-epi-***9*** (25 mg, 24%) as a clear, colourless oil (Found: $M^{+\bullet}$, 268.1306. $C_{14}H_{20}O_5$ requires $M^{+\bullet}$, 268.1311). ^{1}H NMR (300 MHz, $CDCl_3$) δ (compound **9**) spectrum identical with that derived from a pure sample (see below); ^{1}H NMR (300 MHz, $CDCl_3$) δ (compound C8,C9-di-*epi*-**9**) 6.03 (dd, J = 8.1 and 6.0 Hz, 1H), 5.78–5.70 (complex m, 1H), 4.40 (ddd, J = 7.3, 3.2 and 0.8 Hz, 1H), 4.35 (dd, J = 7.3 and 0.8 Hz, 1H), 3.79 (broad d, J = 4.4 Hz, 1H), 3.69 (s, 3H), 3.22–3.14 (complex m, 1H), 2.28 (dd, J = 4.4 and 1.8 Hz, 1H), 1.36 (s, 3H), 1.32 (s, 3H), 1.28 (s, 3H) (signal due to OH proton obscured or overlapping); ^{13}C NMR (75 MHz, $CDCl_3$) δ (compound **9**) spectrum identical with that derived from a pure sample (see below); ^{13}C NMR (75 MHz, $CDCl_3$) δ (compound C8,C9-di-*epi*-**9**) 173.7 (C), 134.9 (CH), 129.7 (CH), 108.5 (C), 78.6 (CH), 77.7 (CH), 75.0 (CH), 52.3 (CH_3), 49.9 (CH), 43.9 (C), 37.5 (CH), 25.4 (CH_3), 24.9 (CH_3), 17.7 (CH_3); MS (EI, 70 eV) *m/z* 268 ($M^{+\bullet}$, 2%), 253 [$(M–CH_3\cdot)^+$, 54], 133 (100), 109 (73), 108 (91), 105 (90), 100 (86), 43 (85).

Concentration of fraction B (R_f = 0.4 in 1:7:12 v/v/v MeOH/ethyl acetate/hexane) gave *compound C9*-epi-***9*** (56 mg, 58%) as a white, crystalline solid, mp = 84–86 °C $[\alpha]_D$ = +26.5 (*c* 0.9, $CHCl_3$) [Found: $(M–CH_3\cdot)^+$, 253.1076; $C_{14}H_{20}O_5$ requires $(M–CH_3\cdot)^+$, 253.1076]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.35–6.29 (m, 1H), 5.74 (dd, J = 8.2 and 1.2 Hz, 1H), 4.17 (dd, J = 7.2 and 3.6 Hz, 1H), 3.83 (dd, J = 7.2 and 1.2 Hz, 1H), 3.72 (d, J = 8.6 Hz, 1H), 3.67 (s, 3H), 3.11–3.06 (complex m, 1H), 2.75 (d, J = 8.6 Hz, 1H), 2.10 (broad s, 1H), 1.37 (s, 3H), 1.31 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0 (C), 131.9 (CH), 131.5 (CH), 109.6 (C), 80.3 (CH), 78.3 (CH), 71.8 (CH), 51.9 (CH_3), 47.8 (CH), 44.9 (C), 36.2 (CH), 25.3 (CH_3), 24.9 (CH_3), 18.2 (CH_3); IR ν_{max} (KBr) 3481, 2977, 2934, 2876, 1737, 1454, 1437, 1371, 1346, 1260, 1203, 1171, 1080, 1056, 1031, 883, 836, 731 cm^{-1}; MS (EI, 70 eV) *m/z* 268 ($M^{+\bullet}$, <1%), 253 [$(M–CH_3\cdot)^+$, 26], 133 (63), 109 (61), 108 (100), 105 (47), 80 (43), 43 (40).

Method B (epimerisation of compound C9-epi-***9***)*: DBU (79 mL, 0.58 mmol) was added to a solution of compound C9-*epi*-**9** (59 mg, 220 μmol) in benzene (1.1 mL) and the reaction mixture heated at 72 °C for 21 h then cooled to 18 °C and diluted with dichloromethane (10 mL). The solution thus obtained was washed with HCl (2 × 10 mL of a 2 M aqueous solution), sodium bicarbonate (1 × 10 mL of a saturated aqueous solution) and brine (1 × 10 mL) before being dried, filtered and concentrated under reduced pressure. The resulting light-yellow solid (52 mg), which was comprised of a 1:3.4 mixture of *β*-hydroxyesters C9-*epi*-**9** and **9** (as determined by ^{1}H NMR analysis), was subjected to column chromatography (silica, 1:7:12 v/v/v MeOH/ethyl acetate/hexane elution) to afford two fractions, A and B.

Concentration of fraction A (R_f = 0.4 in 1:7:12 v/v/v MeOH/ethyl acetate/ hexane) yielded *compound* ***9*** (29 mg, 67% at 73% conversion) as a white, crystalline solid, mp = 132.2–132.4 °C, $[\alpha]_D$ = +47.9 (*c* 1, $CHCl_3$) (Found: $M^{+\bullet}$, 268.1312; C, 62.69, H, 7.54. $C_{14}H_{20}O_5$ requires $M^{+\bullet}$, 268.1311; C, 62.67, H, 7.51%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.28 (ddd, J = 8.1, 6.7 and 0.8 Hz, 1H), 5.77 (dd, J = 8.1 and 1.2 Hz, 1H), 4.23 (ddd, J = 7.3, 3.4 and 1.2 Hz, 1H), 3.91 (dd, J = 3.3 and 1.2 Hz, 1H), 3.87 (dd, J = 7.4 and 1.2 Hz, 1H), 3.74 (s, 3H), 3.20–3.15 (complex m, 1H), 2.33 (t, J = 3.4 Hz, 1H), 1.59 (s, 1H), 1.37 (s, 3H), 1.31 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3 (C), 133.4 (CH), 131.2 (CH), 109.5 (C), 80.6 (CH), 75.7 (CH), 73.0 (CH), 52.4 (CH), 52.3 (CH_3), 44.9 (C), 36.4 (CH), 25.4 (CH_3), 24.9 (CH_3), 17.8 (CH_3); IR ν_{max} (KBr) 3461, 2976, 2927, 2876, 1731, 1374, 1266, 1248, 1206, 1163, 1078, 1066, 1029, 882, 730 cm^{-1}; MS (EI, 70 eV) *m/z* 268 ($M^{+\bullet}$, 8%), 253 [$(M–CH_3\cdot)^+$, 49], 133 (100), 109 (64), 108 (63), 105 (69), 100 (67), 43 (71).

Concentration of fraction B (R_f = 0.4 in 1:7:12 v/v/v MeOH/ethyl acetate/ hexane) afforded *β*-hydroxyester C9-*epi*-**9** (16 mg, 27% recovery) as a white, crystalline solid that was identical, in all respects, with an authentic sample.

3.2.3. Compound 11

Step i: Triethylamine (2.27 g, 22.44 mmol, 1.5 molar equiv.) was added to a magnetically stirred solution of a ca. 4:1 mixture[34] of alcohols **9** and C8,C9-di-*epi*-**9** (4.01 g, 14.96 mmol) in dichloromethane (75 mL) and the resulting mixture cooled to 0 °C then treated, dropwise, with methanesulfonyl chloride (1.89 g, 16.46 mmol, 1.1 molar equiv.). The ensuing mixture was stirred at 0 °C for 1 h then at 18 °C for 4 h after which it was diluted with dichloromethane (25 mL). The resulting solution was washed with ice-cold water (1 × 100 mL), hydrochloric acid

(1 × 100 mL of a 2 M aqueous solution), sodium hydrogen carbonate (1 × 100 mL of a saturated aqueous solution) and brine (1 × 100 mL) before being dried (magnesium sulfate), filtered and concentrated under reduced pressure to give an off-white solid (4.89 g). This material, which was comprised (as determined by ^{1}H NMR analysis) of a ca. 4:1 mixture of the *mesylates of alcohols* ***9*** and *C8,C9-di*-epi-***9***, was and used directly in the step ii of the reaction sequence.

Step ii: DBU (2.40 mL, 16.07 mmol, 2.6 molar equiv.) was added to a solution of the above-mentioned mixture of mesylates (2.14 g, 6.18 mmol) in benzene (30 mL). The resulting mixture was heated to 72 °C for 15 h then cooled to 18 °C and diluted with dichloromethane (20 mL). The ensuing solution was washed with hydrochloric acid (1 × 50 mL of a 2 M aqueous solution), sodium hydrogen carbonate (1 × 50 mL of a saturated aqueous solution) and brine (1 × 50 mL) then dried (magnesium sulfate), filtered and concentrated under reduced pressure. The yellow oil (1.62 g) thus obtained was subjected to column chromatography (silica, 1:7:12 v/v/v MeOH/ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.8) then gave *compound* ***11*** (1.42 g, 92%) as a light-yellow oil, $[\alpha]_D$ = +43.7 (*c* 1, $CHCl_3$) [Found: $(M–CH_3\cdot)^+$, 235.0968; $C_{14}H_{18}O_4$ requires $(M–CH_3\cdot)^+$, 235.0970]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.92 (s, 1H), 6.34–6.28 (complex m, 1H), 5.99–5.95 (complex m, 1H), 4.30–4.25 (complex m, 2H), 3.93–3.89 (complex m, 1H), 3.71 (s, 3H), 1.57 (s, 3H), 1.30 (s, 3H), 1.22 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8 (C), 150.1 (CH), 138.1 (C), 136.2 (CH), 132.1 (CH), 113.2 (C), 82.9 (CH), 79.9 (CH), 51.7 (CH), 47.7 (C), 41.7 (CH_3), 25.8 (CH_3), 25.5 (CH_3), 19.0 (CH_3); IR ν_{max} (KBr) 2977, 2949, 2934, 2905, 1718, 1456, 1437, 1380, 1371, 1263, 1242, 1211, 1162, 1058, 1037, 881, 755, 744, 717 cm^{-1}; MS (EI, 70 eV) *m/z* 235 [$(M–CH_3\cdot)^+$, 33%], 163 (90), 119 (75), 100 (96), 91 (64), 85 (100), 43 (85).

3.2.4. Compound 12

Method A: A solution of α,β-unsaturated ester **11** (897 mg, 3.59 mmol) in THF/MeOH (124 mL of a 7:1 v/v mixture) was cooled to 0 °C and sodium borohydride (489 mg, 12.93 mmol, 3.6 molar equiv.) was then added in one portion. The ensuing mixture was stirred at 0 °C to 18 °C for 4.5 h then re-cooled to 0 °C and quenched with ammonium chloride (100 mL of a saturated aqueous solution). The resulting mixture was extracted with dichloromethane (3 × 50 mL) and the combined organic extracts were washed with brine (1 × 100 mL) before being dried (magnesium sulfate), filtered and concentrated under reduced pressure. The ensuing light-yellow oil was subjected to column chromatography (silica, 1:7:12 v/v/v MeOH/ethyl acetate/hexane elution) to afford two fractions, A and B.

Concentration of fraction A (R_f = 0.8 in 1:7:12 v/v/v MeOH/ethyl acetate/hexane) gave *compound* ***12*** (333 mg, 37%) as a clear, colourless oil, $[\alpha]_D$ = –1.6 (*c* 1, $CHCl_3$) (Found: $M^{+\cdot}$, 252.1357. $C_{14}H_{20}O_4$ requires $M^{+\cdot}$, 252.1362). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.11 (ddd, *J* = 8.1, 6.3 and 0.9 Hz, 1H), 5.83 (dd, *J* = 8.1 and 0.9 Hz, 1H), 4.22 (ddd, *J* = 7.2, 3.3 and 0.9 Hz, 1H), 3.88 (dd, *J* = 7.2 and 1.2 Hz, 1H), 3.69 (s, 3H), 3.16–3.10 (complex m, 1H), 2.47 (ddd, *J* = 11.4, 5.4 and 3.0 Hz, 1H), 1.65 (dd, *J* = 13.5 and 5.4 Hz, 1H), 1.31 (dd, *J* = 13.5 and 11.4 Hz, 1H), 1.29 (s, 3H), 1.25 (s, 3H), 1.23 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8 (C), 136.7 (CH), 130.0 (CH), 107.9 (C), 82.6 (CH), 76.1 (CH), 52.0 (CH_3), 40.8 (CH), 38.5 (C), 37.3 (CH), 31.4 (CH_2), 25.4 (CH_3), 24.9 (CH_3), 21.5 (CH_3); IR ν_{max} (KBr) 2976, 2955, 2936, 2900, 2873, 1733, 1458, 1435, 1374, 1343, 1297, 1265, 1239, 1205, 1165, 1070, 1055, 1021, 997, 885, 724 cm^{-1}; MS (EI, 70 eV) *m/z* 252 ($M^{+\cdot}$, 13%), 237 [$(M–CH_3\cdot)^+$, 44], 221 [$(M–CH_3O\cdot)^+$, 16], 194 (66), 135 (100), 134 (60), 117 (55), 105 (55), 91 (64).

Concentration of fraction B (R_f = 0.8 in 1:7:12 v/v/v MeOH/ethyl acetate/hexane) yielded *compound C9-*epi-***12*** (398 mg, 44%) as a clear, colourless oil, $[\alpha]_D$ = –26.2 (*c* 1, $CHCl_3$) (Found: $M^{+\cdot}$, 252.1363. $C_{14}H_{20}O_4$ requires $M^{+\cdot}$, 252.1362). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.96 (dd, *J* = 8.1 and 6.3 Hz, 1H), 5.88 (dd, *J* = 8.1 and 0.6 Hz, 1H), 4.24 (ddd, *J* = 7.2, 3.3 and 0.9 Hz, 1H), 3.84 (dd, *J* = 7.2 and 1.2 Hz, 1H), 3.65 (s, 3H), 3.23–3.18 (complex m, 1H), 2.50 (ddd, *J* = 10.2, 5.1 and 2.4 Hz, 1H), 1.59 (dd, *J* = 13.5 and 5.1 Hz, 1H), 1.39 (dd, *J* = 13.5 and 10.2 Hz, 1H), 1.30 (s, 3H), 1.26 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6 (C), 136.9 (CH), 127.8 (CH), 108.6 (C), 82.7 (CH), 78.8 (CH), 52.0 (CH_3), 39.6 (CH), 38.1 (C), 37.5 (CH), 32.3 (CH_2), 25.5 (CH_3), 25.0 (CH_3), 21.5 (CH_3); IR ν_{max} (KBr) 2971, 2956, 2931, 2873, 1738, 1373, 1285, 1254, 1203, 1167, 1063, 885, 714 cm^{-1}; MS (EI, 70 eV) *m/z* 252 ($M^{+\cdot}$, 7%), 237 [$(M–CH_3\cdot)^+$, 61], 221 [$(M–CH_3O\cdot)^+$, 27], 194 (84), 162 (84), 135 (100), 134 (83), 117 (70), 105 (70), 100 (81), 93 (70).

Method B: *(epimerisation of compound C9-*epi-***12***)*: A solution of ester C9-*epi*-**12** (368 mg, 1.46 mmol) in MeOH (27 mL) was cooled to 0 °C then sodium methoxide [generated from NaH (105 mg, 4.38 mmol, 3 molar equiv.) and MeOH (18 mL)] was added. After 0.08 h the cooling bath was removed and the reaction mixture heated to 70 °C for 24 h then allowed to cool to 18 °C and quenched with ammonium chloride (20 mL of a saturated aqueous solution). The separated aqueous phase was extracted with dichloromethane (3 × 20 mL) then the combined organic phases were washed with brine (1 × 10 mL) before being dried (magnesium sulfate), filtered and concentrated under reduced pressure to yield a clear, colourless oil. Subjection of this material to column chromatography (silica, 1:7:12 v/v/v MeOH/ethyl acetate/hexane elution) afforded two fractions, A and B.

Concentration of fraction A (R_f = 0.8 in 1:7:12 v/v/v MeOH/ethyl acetate/ hexane) gave ester **12** (62 mg, 36% at 47% conversion) as a clear, colourless oil that was identical, in all respects, with an authentic sample.

Concentration of fraction B (R_f = 0.8 in 1:7:12 v/v/v MeOH/ethyl acetate/ hexane) afforded ester C9-*epi*-**12** (196 mg, 53% recovery) as a clear, colourless oil that was identical, in all respects, with an authentic sample.

3.2.5. Compounds 13 and 14

Method A (reduction of ester 12): A magnetically stirred solution of ester **12** (50 mg, 198 μmol) in dichloromethane (5.20 mL) was cooled to –78 °C then DIBAL (0.34 mL of a 1 M solution in hexane, 340 μmol, 1.7 molar equiv.) was added dropwise. The resulting mixture was stirred at –78 °C for 1.25 h then quenched with potassium sodium tartrate (2 mL of a saturated aqueous solution), warmed to 18 °C and stirred at this temperature for 15 h. The separated aqueous layer was extracted with dichloromethane (3 × 2 mL) and the combined organic phases were then dried (magnesium sulfate), filtered and concentrated under reduced pressure to yield a clear, colourless oil (46 mg). Subjection of this material to column chromatography (silica, 1:4 v/v ethyl acetate/hexane elution) afforded two fractions, A and B.

Concentration of fraction A (R_f = 0.4 in 1:4 v/v ethyl acetate/hexane) gave *aldehyde* ***14*** (13 mg, 30%) as a white, crystalline solid, mp = 59–62 °C, $[\alpha]_D$ = –31.0 (*c* 1, $CHCl_3$) (Found: $M^{+\cdot}$, 222.1253; C, 70.05, H, 8.00. $C_{13}H_{18}O_3$ requires $M^{+\cdot}$, 222.1256; C, 70.25, H, 8.16%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.77 (s, 1H), 6.16 (dd, *J* = 8.1 and 6.8 Hz, 1H), 5.88 (d, *J* = 8.1

Hz, 1H), 4.05 (ddd, J = 7.2, 3.2 and 1.0 Hz, 1H), 3.78 (dd, J = 7.2 and 1.0 Hz, 1H), 3.29–3.27 (complex m, 1H), 2.47 (ddd, J = 11.2, 5.4 and 2.9 Hz, 1H), 1.70 (dd, J = 13.6 and 5.4 Hz, 1H), 1.29 (s, 3H), 1.27 (s, 3H), 1.21 (s, 3H), 1.20 (dd, J = 13.6 and 11.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.4 (CH), 137.5 (CH), 129.5 (CH), 108.1 (C), 82.5 (CH), 75.9 (CH), 49.5 (CH), 38.8 (C), 35.4 (CH), 28.1 (CH_2), 25.4 (CH_3), 24.9 (CH_3), 21.6 (CH_3); IR ν_{max} (KBr) 2975, 2955, 2934, 2872, 1722, 1458, 1373, 1264, 1254, 1208, 1165, 1135, 1071, 1058, 971, 884, 824, 729, 699 cm^{-1}; MS (EI, 70 eV) *m/z* 223 [(M+H)$^+$, 15%], 222 (M$^{+\cdot}$, 5), 207 [(M–CH_3·)$^+$, 46], 164 (63), 135 (98), 117 (65), 93 (67), 92 (100), 91 (63), 43 (75).

Concentration of fraction B (R_f = 0.1 in 1:4 v/v ethyl acetate/hexane) afforded *alcohol* ***13*** (25 mg, 57%) as a clear, colourless oil, $[\alpha]_D$ = –17.3 (*c* 0.9, $CHCl_3$) [Found: (M–CH_3·)$^+$, 209.1179; $C_{13}H_{20}O_3$ requires (M–CH_3·)$^+$, 209.1178]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.16 (dd, J = 8.2 and 6.9 Hz, 1H), 5.80 (d, J = 8.2 Hz, 1H), 4.39 (dd, J = 7.3 and 3.2 Hz, 1H), 3.79 (d, J = 7.3 Hz, 1H), 3.64–3.47 (complex m, 2H), 2.96–2.92 (complex m, 1H), 1.85–1.74 (complex m, 2H), 1.35 (dd, J = 13.3 and 11.1 Hz, 1H), 1.31 (s, 3H), 1.26 (s, 3H), 1.22 (s, 3H), 0.69 (dd, J = 13.3 and 5.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.6 (CH), 131.9 (CH), 107.7 (C), 83.1 (CH), 75.6 (CH), 65.0 (CH_2), 38.6 (CH), 38.4 (C), 35.9 (CH), 33.1 (CH_2), 25.5 (CH_3), 24.9 (CH_3), 21.7 (CH_3); IR ν_{max} (KBr) 3417, 3044, 2970, 2933, 2869, 1457, 1374, 1269, 1246, 1207, 1165, 1075, 1058, 1028, 885, 730, 705, 691, 513 cm^{-1}; MS (EI, 70 eV) *m/z* 209 [(M–CH_3·)$^+$, 25%], 166 (60), 135 (100), 93 (63).

Method B (oxidation of alcohol ***13****)*: A magnetically stirred solution of alcohol **13** (980 mg, 4.37 mmol) in dichloromethane/DMSO (62 mL of a 1:1 v/v mixture) was cooled to 0 °C then treated with triethylamine (3 mL, 21.85 mmol, 5 molar equiv.) and sulfur trioxide·pyridine complex (2.09 g, 13.11 mmol, 3 molar equiv.). The ensuing mixture was stirred at 0 °C for 1 h, diluted with diethyl ether (50 mL) then washed with hydrochloric acid (1 × 10 mL of a 1 M aqueous solution), sodium hydrogen carbonate (1 × 10 mL of a saturated aqueous solution) and brine (1 × 10 mL) before being dried (magnesium sulfate), filtered and concentrated under reduced pressure. The resulting light-orange oil (922 mg) was subjected to column chromatography (silica, 1:5:14 v/v/v MeOH/ethyl acetate/hexane elution) and so giving, after concentration of the appropriate fractions, aldehyde **14** (497 mg, 51%) as a white, crystalline solid that was identical, in all respects, with an authentic sample.

*Method C (reduction of ester C9-*epi*-****12*** *and epimerisation of the resulting aldehyde C9-*epi*-****14****). Step i*: A magnetically stirred solution of ester C9-*epi*-**12** (100 mg, 0.40 mmol) in dichloromethane (10 mL) was cooled to –78 °C then DIBAL (0.48 mL of a 1 M solution in hexane, 0.48 mmol, 1.2 molar equiv.) was added dropwise and the ensuing mixture then stirred at –78 °C for 0.03 h before being quenched with potassium sodium tartrate (5 mL of a saturated solution), warmed to 18 °C and stirred at this temperature for 5 h. The separated aqueous phase was extracted with dichloromethane (3 × 10 mL) then the combined organic phases were washed with brine (1 × 5 mL) then dried (magnesium sulfate), filtered and concentrated under reduced pressure to give a clear, colourless oil. Subjection of this material to column chromatography (silica, 1:4 → 1:1 v/v ethyl acetate/hexane gradient elution) afforded two fractions, A and B.

Concentration of fraction A (R_f = 0.4 in 1:4 v/v ethyl acetate/hexane) gave aldehyde **14** (4 mg, 5%) as a white, crystalline solid. This material was identical, in all respects, with an authentic sample.

Concentration of fraction B (R_f = 0.3 in 1:4 v/v ethyl acetate/hexane) afforded *compound C9-*epi*-****14*** (58 mg, 65%) as a clear, colourless oil, $[\alpha]_D$ = +15.3 (*c* 1.15, $CHCl_3$) [Found: (M–CH_3·)$^+$, 207.1026; $C_{13}H_{18}O_3$ requires (M–CH_3·)$^+$, 207.1021]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.49 (d, J = 1.1 Hz, 1H), 5.95–5.86 (complex m, 2H), 4.32 (ddd, J = 7.2, 3.3 and 1.0 Hz, 1H), 3.89 (dd, J = 7.2 and 1.0 Hz, 1H), 3.25–3.20 (complex m, 1H), 2.44 (dddd, J = 9.9, 4.7, 2.2 and 1.0 Hz, 1H), 1.64 (dd, J = 13.6 and 4.7 Hz, 1H), 1.31 (dd, J = 13.6 and 9.9 Hz, 1H), 1.30 (s, 3H), 1.28 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.9 (CH), 137.9 (CH), 127.1 (CH), 108.7 (C), 83.1 (CH), 79.0 (CH), 48.0 (CH), 38.4 (C), 35.9 (CH), 29.6 (CH_2), 25.4 (CH_3), 25.0 (CH_3), 21.5 (CH_3); IR ν_{max} (KBr) 2975, 2954, 2932, 2873, 1726, 1458, 1374, 1277, 1251, 1209, 1166, 1121, 1068, 1023, 884, 728 cm^{-1}; MS (EI, 70 eV) *m/z* 223 [(M+H)$^+$, 20%], 222 (M$^{+\cdot}$, 1), 207 [(M–CH_3·)$^+$, 16], 135 (79), 117 (52), 100 (51), 93 (49), 91 (63), 85 (46), 43 (100).

Step ii: DBU (26 µl, 171 µmol, 1 molar equiv.) was added to a magnetically stirred solution of aldehyde C9-*epi*-**14** (38 mg, 171 µmol) in benzene (1 mL) and the resulting mixture heated at 70 °C for 16 h, then cooled to 18 °C and diluted with dichloromethane (4 mL) before being washed successively with hydrochloric acid (1 × 2 mL of a 2 M aqueous solution), sodium hydrogen carbonate (1 × 2 mL of a saturated aqueous solution) and brine (1 × 2 mL) then dried (magnesium sulfate), filtered and concentrated under reduced pressure. ^{1}H NMR analysis of the resulting yellow oil (33 mg) established that this was comprised of a ca. 1:4.8 mixture of aldehydes C9-*epi*-**14** and **14**.

3.2.6. Compound ***15***

$MePPh_3Br$ was dried at 100 °C for 15 h then cooled and stored under nitrogen. Some of the dried material (2.05 g, 5.73 mmol, 3.0 molar equiv.) was stirred in THF (19.1 mL) then cooled to 0 °C and treated, dropwise, with NaHMDS (4.58 mL of a 1 M solution in THF, 4.58 mmol, 2.4 molar equiv.). The resulting mixture was stirred at 0 °C for 2.5 h and the bright-yellow reaction mixture so-formed was treated, dropwise, with a solution of aldehyde **14** (424 mg, 1.91 mmol) in THF (8.50 mL). Stirring was continued at 0 °C for 2 h then the reaction mixture was quenched with ammonium chloride (10 mL of a saturated aqueous solution) and diluted with dichloromethane (10 mL). The separated aqueous phase was extracted with dichloromethane (3 × 20 mL) then the combined organic phases were washed with brine (1 × 10 mL) before being dried (magnesium sulfate), filtered and concentrated under reduced pressure. The orange oil thus obtained was subjected to column chromatography (silica, 1:9 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.5) then gave olefin **15** (253 mg, 60%) as a clear, colourless oil, $[\alpha]_D$ = –45.3 (*c* 0.55, $CHCl_3$) [Found: (M–H·)$^+$, 219.1382; $C_{14}H_{20}O_2$ requires (M–H·)$^+$, 219.1385]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.17 (ddd, J = 7.8, 6.3 and 1.0 Hz, 1H), 5.83 (ddd, J = 17.2, 10.3 and 6.9 Hz, 1H), 5.79 (dd, J = 7.8 and 1.0 Hz, 1H), 5.11–5.01 (complex m, 2H), 4.36 (ddd, J = 7.4, 3.3 and 1.0 Hz, 1H), 3.81 (dd, J = 7.4 and 1.0 Hz, 1H), 2.80–2.74 (complex m, 1H), 2.29–2.18 (complex m, 1H), 1.39 (dd, J = 13.4 and 11.0 Hz, 1H), 1.32 (s, 3H), 1.26 (s, 3H), 1.24 (s, 3H), 1.01 (dd, J = 13.4 and 5.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.0 (CH), 135.4 (CH), 131.9 (CH), 114.6 (CH_2), 107.6 (C), 83.3 (CH), 75.9 (CH), 40.8 (CH), 39.4 (CH), 38.7 (C), 34.6 (CH_2), 25.5 (CH_3), 24.9 (CH_3), 21.8 (CH_3); IR ν_{max} (KBr) 3045, 2976, 2952, 2937, 2903, 2869, 1638, 1457, 1378, 1371, 1262, 1233, 1207, 1165, 1069, 1056, 995, 912, 885, 861, 809, 729, 707 cm^{-1}; MS (EI, 70 eV) *m/z* 220 (M$^{+\cdot}$, 18%), 219 [(M–H·)$^+$, 38], 205 [(M–CH_3·)$^+$, 11], 163 (68), 105 (64), 57 (100), 43 (46).

3.2.7. Compound 16

DOWEX-50 was activated by washing it twice with MeOH, twice with hydrochloric acid (2 M aqueous solution) and, finally, twice with water. The activated resin (269 mg) thus obtained was added to a magnetically stirred solution of acetonide **15** (269 mg, 1.22 mmol) in MeOH/water (6 mL of a 5:1 v/v mixture) and the resulting suspension heated in an oil bath maintained at 110 °C. After six days the reaction mixture was cooled, filtered and the DOWEX washed three times with MeOH. The combined filtrates were concentrated under reduced pressure. The resin was also washed twice with dichloromethane and the filtrate added to the concentrated residue which was then washed with sodium chloride (1 × 10 mL of a 1.5 M aqueous solution). The separated aqueous phase was extracted with dichloromethane (3 × 10 mL) then the combined organic phases were dried (magnesium sulfate), filtered and concentrated under reduced pressure. The orange oil (201 mg) thus obtained was subjected to column chromatography (silica, 1:4 → 1:1 v/v ethyl acetate/hexane gradient elution) and concentration of the appropriate fractions (R_f = 0.5 in 1:1 v/v ethyl acetate/hexane) then gave diol **15** (146 mg, 66%) as a clear, colourless oil, $[\alpha]_D$ = –76.1 (*c* 1, $CHCl_3$) (Found: $M^{+\cdot}$, 180.1144. $C_{11}H_{16}O_2$ requires $M^{+\cdot}$, 180.1150). ^1H NMR (300 MHz, $CDCl_3$) δ 6.32 (ddd, *J* = 8.1, 7.0 and 0.8 Hz, 1H), 5.90 (dd, *J* = 8.1 and 0.8 Hz, 1H), 5.82 (ddd, *J* = 17.0, 10.3 and 6.7 Hz, 1H), 5.10–5.01 (complex m, 2H), 4.05 (ddd, *J* = 7.6, 2.5 and 0.8 Hz, 1H), 3.44 (dd, *J* = 7.6 and 0.8 Hz, 1H), 2.80 (broad s, 2H), 2.67–2.62 (complex m, 1H), 2.20–2.09 (complex m, 1H), 1.38 (dd, *J* = 13.5 and 11.2 Hz, 1H), 1.23 (s, 3H), 1.06 (dd, *J* = 13.5 and 6.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.8 (CH), 136.6 (CH), 133.4 (CH), 114.9 (CH_2), 75.6 (CH), 67.9 (CH), 43.8 (CH), 40.2 (C), 40.0 (CH), 35.3 (CH_2), 21.6 (CH_3); IR ν_{max} (KBr) 3374, 2928, 2869, 1637, 1457, 1403, 1372, 1065, 1031, 994, 959, 910, 726, 703, 601 cm^{-1}; MS (EI, 70 eV) *m/z* 180 ($M^{+\cdot}$, 5%), 120 (97), 105 (100), 92 (72), 91 (53).

3.2.8. Compound 17

A magnetically stirred solution of diol **16** (146 mg, 0.81 mmol) in dichloromethane (19.50 mL) was cooled to 0 °C then *p*-TsOH•H_2O (339 mg, 1.78 mmol, 2.2 molar equiv.) was added followed by 4-AcNH-TEMPO (380 mg, 1.78 mmol, 2.2 molar equiv.) and the mixture thus obtained was warmed to 18 °C. After 17 h at the latter temperature, the reaction mixture was quenched with sodium hydrogen carbonate (10 mL of a saturated aqueous solution) and extracted with dichloromethane (3 × 20 mL). The combined organic extracts were washed with brine (1 × 10 mL) before being dried (magnesium sulfate), filtered and concentrated under reduced pressure. The resulting orange semi-solid (533 mg) was subjected to column chromatography (silica, 1:4 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.3) then gave *acyloin* ***17*** (118 mg, 81%) as a clear, colourless oil, $[\alpha]_D$ = +346.5 (*c* 0.65, $CHCl_3$) (Found: $M^{+\cdot}$, 178.0986. $C_{11}H_{14}O_2$ requires $M^{+\cdot}$, 178.0994). ^1H NMR (300 MHz, $CDCl_3$) δ 6.19 (dd, *J* = 7.7 and 6.6 Hz, 1H), 6.11 (d, *J* = 7.7 Hz, 1H), 5.68 (ddd, *J* = 17.0, 10.3 and 7.3 Hz, 1H), 5.10–4.98 (complex m, 2H), 3.37 (s, 1H), 3.20 (dd, *J* = 6.6 and 2.2 Hz, 1H), 2.73 (broad s, 1H), 2.61–2.50 (complex m, 1H), 1.80 (dd, *J* = 13.4 and 11.7 Hz, 1H), 1.43 (dd, *J* = 13.4 and 4.7 Hz, 1H), 1.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.6 (C), 140.7 (CH), 140.5 (CH), 126.9 (CH), 115.1 (CH_2), 75.1 (CH), 52.7 (CH), 42.2 (C), 39.0 (CH), 37.9 (CH_2), 20.0 (CH_3); IR ν_{max} (KBr) 3448, 2970, 2954, 2931, 2869, 1725, 1639, 1457, 1115, 1068, 990, 915, 776, 709 cm^{-1}; MS (EI, 70 eV) *m/z* 178 ($M^{+\cdot}$, 8%), 106 (72), 105 (100), 91 (71), 79 (70), 43 (73), 39 (64), 32 (67).

3.2.9. Compound 18

A magnetically stirred solution of acyloin **17** (118 mg, 0.66 mmol) in dichloromethane (21 mL) was cooled to 0 °C then treated with triethylamine (0.46 mL, 3.30 mmol, 5 molar equiv.), DMAP (9 mg, 0.07 mmol, 10 mol%) and benzoyl chloride (0.15 mL, 1.32 mmol, 2 molar equiv.). The ensuing mixture was allowed to warm to 18 °C and after 16 h it was quenched with sodium hydrogen carbonate (10 mL of a saturated aqueous solution). The separated aqueous phase was extracted with dichloromethane (3 × 20 mL) then the combined organic extracts were washed with brine (1 × 10 mL) before being dried (magnesium sulfate), filtered and concentrated under reduced pressure. The yellow semi-solid (301 mg) thus obtained was subjected to column chromatography (silica, 1:4 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions gave (R_f = 0.6) *keto-ester* ***18*** (199 mg, 0.71 mmol, quant.) as a clear, colourless oil, $[\alpha]_D$ = +255.9 (*c* 1, $CHCl_3$) (Found: $M^{+\cdot}$, 282.1255. $C_{18}H_{18}O_3$ requires $M^{+\cdot}$, 282.1256). ^1H NMR (300 MHz, $CDCl_3$) δ 8.02–7.98 (complex m, 2H), 7.59–7.52 (complex m, 1H), 7.46–7.39 (complex m, 2H), 6.32 (dd, *J* = 7.8 and 6.7 Hz, 1H), 6.20 (d, *J* = 7.8 Hz, 1H), 5.76 (ddd, *J* = 17.2, 10.3 and 7.4 Hz, 1H), 5.16–5.05 (complex m, 2H), 5.08 (s, 1H), 3.26 (ddd, *J* = 6.7, 2.9 and 1.1 Hz, 1H), 2.67–2.56 (complex m, 1H), 1.89 (dd, *J* = 13.6 and 11.5 Hz, 1H), 1.62 (dd, *J* = 13.6 and 4.9 Hz, 1H), 1.22 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.3 (C), 166.1 (C), 140.0 (CH), 139.8 (CH), 133.2 (CH), 129.9 (CH), 129.4 (C), 128.3 (CH), 127.6 (CH), 115.6 (CH_2), 74.5 (CH), 53.5 (CH), 41.3 (C), 39.5 (CH), 37.5 (CH_2), 20.1 (CH_3); IR ν_{max} (KBr) 2965, 2925, 2869, 2853, 1741, 1724, 1451, 1328, 1266, 1254, 1177, 1111, 1070, 1029, 921, 708 cm^{-1}; MS (EI, 70 eV) *m/z* 282 ($M^{+\cdot}$, 21%), 160 (37), 132 (62), 120 (41), 106 (76), 105 (100), 91 (30), 77 (89), 51 (43).

3.2.10. Compound 19

A magnetically stirred and deoxygenated solution of keto-ester **18** (186 mg, 0.66 mmol) and acetophenone (0.23 mL, 1.98 mmol, 3 molar equiv.) in acetone (300 mL) was placed in a quartex immersion well photoreactor (Ace Glass Inc., 500 mL) equipped with a Pyrex filter. The mixture was subjected to irradiation, at 18 °C, with a Hanovia 450W medium pressure quartz mercury-vapour lamp. After 4.67 h the reaction mixture was removed from the photoreactor and concentrated under reduced pressure to give a yellow oil (459 mg) that was subjected to column chromatography (silica, 1:4 v/v ethyl acetate/hexane elution) and thereby affording two fractions, A and B.

Concentration of fraction A (R_f = 0.5) yielded a mixture of acetophenone and the *C4-α-form of diquinane* ***19*** (49 mg) as a clear, colourless oil. Resubjection of the material to flash chromatography (silica, 1:9 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.2) then gave the *C4-α-form of diquinane* ***19*** (29 mg, 15%) as a clear, colourless oil $[\alpha]_D$ = +139.1 (*c* 0.9, $CHCl_3$) (Found: $M^{+\cdot}$, 282.1260. $C_{18}H_{18}O_3$ requires $M^{+\cdot}$, 282.1256). ^1H NMR (300 MHz, $CDCl_3$) δ 8.06–8.02 (complex m, 2H), 7.60–7.54 (complex m, 1H), 7.47–7.40 (complex m, 2H), 5.82 (ddd, *J* = 17.3, 10.4 and 5.6 Hz, 1H), 5.19–5.02 (complex m, 2H), 5.08 (broad s, 1H), 3.46–3.35 (complex m, 1H), 2.61 (ddd, *J* = 6.0, 5.1 and 1.0 Hz, 1H), 2.43 (dd, *J* = 13.5 and 11.0 Hz, 1H), 2.33 (m, 1H), 2.23 (m, 1H), 1.89 (dt, *J* = 13.5 and 1.4 Hz, 1H), 1.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.9 (C), 165.6 (C), 139.5 (CH), 133.2 (CH), 129.9 (CH), 129.5 (C), 128.4 (CH), 115.8 (CH_2), 83.5 (CH), 49.9 (C), 49.8 (CH_2), 43.0 (CH), 42.0 (CH), 39.8 (CH), 38.4 (CH), 19.3 (CH_3); IR ν_{max} (KBr) 2970, 2935, 2874, 1722, 1451, 1266 (broad), 1177, 1107, 1094, 1069, 1026, 990, 957, 915, 852, 709, 668 cm^{-1}; MS (EI, 70 eV) *m/z* 282 ($M^{+\cdot}$, 2%), 160 (25), 132 (45), 106 (55), 105 (71), 91 (37), 77 (100).

Concentration of fraction B (R_f = 0.5) gave the *C4-β-form of diquinane* ***19*** (30 mg, 17%) as a clear, colourless oil, $[\alpha]_D$ = +60.2 (*c* 0.6, $CHCl_3$) (Found: $M^{+\cdot}$, 282.1256. $C_{18}H_{18}O_3$ requires $M^{+\cdot}$, 282.1256). ^1H NMR (300 MHz, $CDCl_3$) δ 8.07–8.03 (complex m, 2H), 7.61–7.55 (complex m, 1H), 7.48–7.42 (complex m, 2H), 5.80 (ddd, *J* = 17.0, 10.3 and 7.0 Hz, 1H), 5.44 (t, *J* = 1.5 Hz, 1H), 5.11 (dt, *J* = 17.0 and 1.5 Hz, 1H), 5.01 (dt, 10.3 and 1.5 Hz, 1H), 3.45–3.35 (complex m, 1H), 2.37 (dd, *J* = 5.9 and 4.8 Hz, 1H), 2.28 (dt, *J* = 9.8 and 5.9 Hz, 1H), 2.12 (ddd, *J* = 14.0, 11.0 and 1.5 Hz, 1H), 2.05–1.98 (complex m, 2H), 1.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.1 (C), 165.4 (C), 139.2 (CH), 133.3 (CH), 129.9 (CH), 129.3 (C), 128.4 (CH), 115.3 (CH_2), 82.1 (CH), 49.3 (C), 44.2 (CH), 43.5 (CH_2), 36.4 (CH), 35.8 (CH), 32.6 (CH), 24.3 (CH_3); IR ν_{max} (KBr) 2959, 1739, 1724, 1452, 1331, 1269, 1248, 1177, 1113, 1097, 1071, 1026, 1000, 916, 850, 709 cm^{-1}; MS (EI, 70 eV) *m/z* 282 ($M^{+\cdot}$, 11%), 160 (37), 132 (49), 106 (52), 105 (100), 77 (69).

3.2.11. Compound 20

A magnetically stirred solution of the α- and β-epimeric forms of compound **19** (296 mg, 1.05 mmol) in THF (10.5 mL) containing MeOH (5.3 mL) was cooled to –78 °C then samarium diiodide (23.1 mL of a 0.1 M solution in THF, 2.31 mmol, 2.2 molar equiv.) was added dropwise. Stirring was continued at –78 °C for 0.08 h then the reaction mixture was quenched with potassium carbonate (20 mL of a saturated aqueous solution) before being allowed to slowly warm to 18 °C. The separated aqueous phase was extracted with diethyl ether (3 × 50 mL) and the combined organic phases were washed with brine (1 × 20 mL) then dried (magnesium sulfate), filtered and concentrated under reduced pressure. The yellow oil (289 mg) thus obtained was subjected to column chromatography (silica, 1:39 v/v ethyl acetate/ dichloromethane elution) and concentration of the appropriate fractions (R_f = 0.5) gave *diquinane* ***20*** (93 mg, 54%) as a clear, colourless oil, $[\alpha]_D$ = +74.0 (*c* 0.6, $CHCl_3$) (Found: $M^{+\cdot}$, 162.1044. $C_{11}H_{14}O$ requires $M^{+\cdot}$, 162.1045). ^1H NMR (300 MHz, $CDCl_3$) δ 5.82 (ddd, *J* = 17.2, 10.3 and 5.8 Hz, 1H), 5.08 (dt, *J* = 17.2 and 1.7 Hz, 1H), 4.97 (dt, *J* 10.3 and 1.7 Hz, 1H), 3.37–3.26 (complex m, 1H), 2.45 (ddd, *J* = 6.3, 4.9 and 0.8 Hz, 1H), 2.33–2.22 (complex m, 2H), 2.20–2.04 (complex m, 2H), 1.96 (m, 1H), 1.63 (d, *J* = 12.6 Hz, 1H), 1.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.5 (C), 139.9 (CH), 115.0 (CH_2), 55.0 (CH_2), 52.4 (CH_2), 46.3 (C), 43.4 (CH), 42.3 (CH), 39.6 (CH), 36.8 (CH), 25.7 (CH_3); IR ν_{max} (KBr) 2954, 2928, 2870, 1724, 1454, 1407, 1331, 1313, 1250, 1197, 1096, 989, 965, 914, 885, 871 cm^{-1}; MS (EI, 70 eV) *m/z* 162 ($M^{+\cdot}$, 11%), 120 (50), 105 (100), 77 (45).

3.2.12. Compound 21

A magnetically stirred solution of diquinane **20** (52 mg, 321 μmol) in acetone/water (2 mL of a 1:1 v/v mixture) was cooled to 0 °C then *N*-methylmorpholine *N*-oxide (45 mg, 385 μmol, 1.2 molar equiv.) and osmium tetroxide (1.22 mL of a 0.1 M solution in *t*-butanol, 122 μmol, 0.38 molar equiv.) were added. The ensuing mixture was allowed to warm to 18 °C and after 4.5 h at this temperature it was quenched with sodium hydrogensulfite (4 mL of a saturated aqueous solution) then stirred at 18 °C for another hour. The resulting mixture was diluted with diethyl ether (4 mL) and just enough water to dissolve any solids. Solid sodium chloride was then added to saturate the aqueous phase which, after separation, was extracted with diethyl ether (3 × 10 mL) then dichloromethane (3 × 10 mL). The combined organic extracts were dried (magnesium sulfate), filtered and concentrated under reduced pressure. Subjection of the resulting clear, colourless oil to column chromatography (silica, ethyl acetate → 1:9 v/v MeOH/ethyl acetate gradient elution) and concentration of the appropriate fractions (R_f = 0.4 in 1:9 v/v methanol/ethyl acetate) then gave a 1:1 mixture of the *epimeric forms of diol* ***22*** (30 mg, 48%) as a clear, colourless oil (Found: $M^{+\cdot}$, 196.1098. $C_{11}H_{16}O_3$ requires $M^{+\cdot}$, 196.1099). ^1H NMR (300 MHz, $CDCl_3$) δ 3.84 (dd, *J* = 11.3 and 2.2 Hz, 0.5H), 3.66–3.58 (complex m, 0.5H), 3.50 (broad s, 2H), 3.45 (dd, *J* = 11.3 and 7.4 Hz, 0.5H), 3.40–3.30 (complex m, 1.5H), 2.71–2.55 (complex m, 1H), 2.54–2.48 (complex m, 1H), 2.43–2.30 (complex m, 1H), 2.27–1.80 (complex m, 5H), 1.37 (s, 1.5H), 1.36 (s, 1.5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.6 (C), 217.4 (C), 74.2 (CH), 74.1 (CH), 66.2 (CH_2), 65.4 (CH_2), 56.4 (CH_2), 56.0 (CH_2), 48.8 (CH_2), 48.6 (CH_2), 46.6 (C), 46.2 (C), 43.8 (2xCH), 42.9 (CH), 42.8 (CH), 39.3 (CH), 39.1 (CH), 37.1 (CH), 35.4 (CH), 25.9 (CH_3), 25.8 (CH_3); IR ν_{max} (KBr) 3405, 2951, 2928, 2871, 1709, 1454, 1408, 1379, 1360, 1335, 1312, 1254, 1200, 1161, 1101, 1076, 1041, 964, 920, 879, 813, 735 cm^{-1}; MS (EI, 70 eV) *m/z* 196 ($M^{+\cdot}$, 2%), 178 [$(M–H_2O\cdot)^+$, 14], 165 (75), 136 (96), 95 (94), 94 (88), 93 (100), 91 (77), 43 (75).

3.2.13. Compound 22

Dibutyltin(IV)oxide (8 mg, 32 μmol, 20 mole %) then triethylamine (21 μl, 153 μmol, 1 molar equiv.) were added to a magnetically stirred solution of a 1:1 mixture of the epimeric forms of diol **21** (30 mg, 153 μmol) in dichloromethane (0.45 mL). Stirring was continued at 18 °C for 0.17 h then a solution of *p*-toluenesulfonyl chloride (29 mg, 152 μmol, 1 molar equiv.) in dichloromethane (ca. 0.25 mL) was added dropwise over a period of 0.17 h. After 5 h at 18 °C the reaction mixture was diluted with dichloromethane (0.4 mL) then filtered through a plug of Celite™ and the filtrate concentrated under reduced pressure to give a light-yellow oil (67 mg). This was subjected to column chromatography (silica, 1:3:6 v/v/v MeOH/ethyl acetate/hexane elution) and thus affording three fractions, A, B and C.

Concentration of fraction A (R_f = 0.4) yielded the *C1′R-epimeric form of mono-tosylate* ***22*** (9 mg, 17%) as a clear, colourless oil, $[\alpha]_D$ = +26.4 (*c* 0.64, $CHCl_3$) (Found: $M^{+\cdot}$, 350.1182. $C_{18}H_{22}O_5S$ requires $M^{+\cdot}$, 350.1188). ^1H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 4.17 (dd, *J* = 10.4 and 4.6 Hz, 1H), 4.13 (dd, *J* = 10.4 and 2.7 Hz, 1H), 3.56–3.50 (complex m, 1H), 2.77–2.71 (complex m, 1H), 2.49 (dd, *J* = 5.9 and 5.3 Hz, 1H), 2.45 (s, 3H), 2.37 (ddd, *J* = 17.8, 2.3 and 1.2 Hz, 1H), 2.26–2.12 (complex m, 2H), 1.94–1.88 (complex m, 1H), 1.85 (dd, *J* = 9.8 and 5.3 Hz, 1H), 1.81 (d, *J* = 13.4 Hz, 1H), 1.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.3 (C), 145.1 (C), 132.4 (C), 130.0 (CH), 128.0 (CH), 72.7 (CH_2), 71.4 (CH), 56.0 (CH_2), 48.6 (CH_2), 46.3 (C), 43.8 (CH), 42.3 (CH), 38.9 (CH), 34.6 (CH), 25.9 (CH_3), 21.7 (CH_3); IR ν_{max} (KBr) 3418, 2954, 2926, 2870, 1715, 1598, 1453, 1406, 1357, 1309, 1189, 1176, 1098, 1019, 972, 957, 917, 878, 855, 814, 667, 555 cm^{-1}; MS (EI, 70 eV) *m/z* 350 ($M^{+\cdot}$, 1%), 165 (31), 155 (33), 136 (100), 105 (45), 93 (51), 91 (80).

Concentration of fraction B (R_f = 0.35) afforded a ca. 1:1.5 mixture of the C1′*R*- and C1′*S*-epimeric forms of mono-tosylate **22** (29 mg, 54%) as a clear, colourless oil.

Concentration of fraction C (R_f = 0.3) gave *C1′S-epimeric form of mono-tosylate* ***22*** (3 mg, 6%) as a clear, colourless oil, $[\alpha]_D$ = +25.7 (*c* 0.35, $CHCl_3$) (Found: $M^{+\cdot}$, 350.1188. $C_{18}H_{22}O_5S$ requires $M^{+\cdot}$, 350.1188). ^1H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 4.06 (dd, *J* = 10.5 and 2.7 Hz, 1H), 3.90 (dd, *J* = 10.5 and 6.3 Hz, 1H), 3.58–3.52 (complex m, 1H), 2.73–2.66 (complex m, 1H), 2.55–2.48 (complex m, 2H), 2.45 (s, 3H), 2.40 (dd, *J* 17.8 and 2.2 Hz, 1H), 2.18–2.02 (complex m, 3H), 1.99 (dd, *J* = 9.5 and 5.2 Hz, 1H), 1.37 (s, 3H), 1.33 (d, *J* = 13.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.3 (C), 145.1 (C), 132.7 (C), 129.9 (CH), 127.9 (CH), 73.1 (CH_2), 71.3 (CH), 56.4 (CH_2), 48.6 (CH_2), 46.6 (C),

43.6 (CH), 42.1 (CH), 39.0 (CH), 35.7 (CH), 25.8 (CH_3), 21.7 (CH_3); IR ν_{max} (KBr) 3420, 2956, 2918, 2870, 2850, 1712, 1598, 1453, 1358, 1312, 1189, 1176, 1097, 972, 957, 946, 918, 880, 853, 815, 667, 555 cm^{-1}; MS (EI, 70 eV) *m/z* 350 ($M^{+\cdot}$, 5%), 165 (47), 136 (100), 93 (68), 91 (95), 43 (67), 32 (48).

3.2.14. Compounds 23 and 24

Method A: A magnetically stirred solution of a ca. 1:1.5 mixture of the C1′*R*- and C1′*S*-epimeric forms of mono-tosylate **22** (29 mg, 83 μmol) in dichloromethane (2.9 mL) was cooled to 0 °C then triethylamine (58 μL, 414 μmol, 5 molar equiv.) was added followed by DMAP (834 μg, 8.28 μmol, 10 mole %) and benzoyl chloride (20.7 μL, 166 μmol, 2 molar equiv.). The resulting mixture was allowed to warm to 18 °C then stirred at this temperature for 14 h before being quenched with sodium hydrogen carbonate (1 mL of a saturated aqueous solution). The separated aqueous phase was extracted with dichloromethane (5 × 2 mL) then the combined organic phases were dried (magnesium sulfate), filtered and concentrated under reduced pressure. The clear, colourless oil (51 mg) thus obtained was subjected to column chromatography (silica, 1:3:6 v/v/v MeOH/ethyl acetate/hexane elution) to afford two fractions, A and B.

Concentration of fraction A (R_f = 0.5) gave *compound 24* (15 mg, 40%) as a clear, colourless, $[\alpha]_D$ = +14.2 (*c* 0.38, $CHCl_3$) (Found: $M^{+\cdot}$, 454.1447. $C_{25}H_{26}O_6S$ requires $M^{+\cdot}$, 454.1450). ^1H NMR (500 MHz, $CDCl_3$) δ 7.92 (dd, *J* = 8.3 and 1.2 Hz, 2H), 7.73 (d, *J* = 8.3 Hz, 2H), 7.59–7.55 (complex m, 1H), 7.42 (dd, *J* = 8.3 Hz, 2H), 7.20 (d, *J* = 8.3 Hz, 2H), 4.98 (m, *J* = 11.1 Hz, 1H), 4.44 (dd, *J* = 11.2 and 2.6 Hz, 1H), 4.24 (dd, *J* = 11.2 and 2.2 Hz, 1H), 3.24 (m, 1H), 2.54 (dd, *J* = 5.9 and 5.3 Hz, 1H), 2.40 (dd, *J* = 18.1 and 1.0 Hz, 1H), 2.34 (s, 3H), 2.30 (d, *J* = 18.1 Hz, 1H), 2.20 (ddd, *J* = 13.2, 10.7 and 2.0 Hz, 1H), 2.11–2.06 (complex m, 1H), 1.95 (dd, *J* = 9.8 and 5.3 Hz, 1H), 1.55 (d, *J* = 13.2 Hz, 1H), 1.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.8 (C), 165.5 (C), 144.9 (C), 133.3 (CH), 132.3 (C), 129.9 (CH), 129.8 (CH), 129.5 (C), 128.3 (CH), 127.9 (CH), 73.0 (CH), 69.7 (CH_2), 55.3 (CH_2), 48.7 (CH_2), 46.5 (C), 42.3 (CH), 41.1 (CH), 39.0 (CH), 34.0 (CH), 25.8 (CH_3), 21.6 (CH_3); IR ν_{max} (KBr) 2956, 2927, 1720, 1599, 1452, 1364, 1270, 1190, 1177, 1109, 1097, 1070, 1026, 962, 946, 922, 881, 814, 793, 714, 667, 554 cm^{-1}; MS (EI, 70 eV) *m/z* 454 ($M^{+\cdot}$, 4%), 149 (18), 118 (55), 105 (100), 91 (27), 77 (34), 57 (32), 43 (35).

Concentration of fraction B (R_f = 0.4) afforded *compound 23* (21 mg, 55%) as a white, crystalline solid, mp = 134–139 °C, (Found: $M^{+\cdot}$, 454.1448. $C_{25}H_{26}O_6S$ requires $M^{+\cdot}$, 454.1450). ^1H NMR (300 MHz, $CDCl_3$) δ 7.97–7.93 (complex m, 2H), 7.70–7.66 (complex m, 2H), 7.60–7.54 (complex m, 1H), 7.45–7.40 (complex m, 2H), 7.15–7.12 (complex m, 2H), 4.87 (dt, *J* = 11.2 and 2.9 Hz, 1H), 4.31 (dd, *J* = 11.4 and 2.9 Hz, 1H), 4.17 (dd, *J* = 11.4 and 2.9 Hz, 1H), 3.34 (m, 1H), 2.51 (t, *J* = 5.4 Hz, 1H), 2.44–2.30 (complex m, partially concealed, 1H), 2.34–2.24 (complex m, partially concealed, 1H), 2.30 (s, 3H), 2.15–2.07 (complex m, partially concealed, 1H), 2.07 (d, *J* = 17.0 Hz, 1H), 1.87 (dd, *J* = 10.2 and 5.4 Hz, 1H), 1.44 (d, *J* = 13.2 Hz, 1H), 1.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.7 (C), 165.1 (C), 145.0 (C), 133.2 (CH), 132.1 (C), 129.9 (CH), 129.8 (CH), 129.5 (C), 128.2 (CH), 127.8 (CH), 73.2 (CH), 69.4 (CH_2), 56.2 (CH_2), 47.8 (CH_2), 46.5 (C), 42.1 (CH), 40.9 (CH), 38.9 (CH), 35.6 (CH), 25.8 (CH_3), 21.6 (CH_3); IR ν_{max} (KBr) 2956, 1723, 1599, 1451, 1361, 1312, 1266, 1189, 1176, 1109, 1096, 1069, 1025, 957, 946, 921, 884, 839, 814, 713, 667, 554 cm^{-1}; MS (EI, 70 eV) *m/z* 454 ($M^{+\cdot}$, 3%), 283 (16), 118 (72), 105 (100), 91 (36), 77 (41).

Method B: A magnetically stirred solution of the C1′*R*-epimeric form of monotosylate **22** (7 mg, 20 μmol) in dichloromethane (0.7 mL) was treated in the same way as described immediately above. The clear, colourless oil (5 mg) thus obtained was subjected to column chromatography (silica, 1:3:6 v/v/v MeOH/ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.5) then gave *compound 24* (3 mg, 35%) as a white, crystalline solid. This material was identical, in all respects, with an authentic sample.

3.2.15. Compound 25

A solution of diquinane **23** (21 mg, 46 μmol) in THF/MeOH (0.9 mL of a 2:1 v/v mixture) was cooled to –78 °C and samarium diiodide (0.55 mL of a 0.1 M solution in THF, 55 μmol, 1.2 molar equiv.) was added dropwise over 0.08 h. The resulting mixture was stirred at –78 °C until the initial blue colour associated with the reaction mixture had turned yellow (ca. 0.4 h) then more samarium diiodide (0.55 mL of a 0.1 M solution in THF, 55 μmol, 1.2 molar equiv.) was added dropwise and the reaction warmed to 0 °C at which point sufficient additional samarium diiodide was added to re-establish a deep-blue colour. The reaction mixture was then warmed to 18 °C and stirred at this temperature until the blue colour had faded. This procedure was repeated twice more at 18 °C until the starting material had been consumed as determined by TLC analysis. The reaction mixture was then quenched with potassium carbonate (1 mL of a saturated aqueous solution) and the separated aqueous phase extracted with diethyl ether (3 × 5 mL) and then with dichloromethane (3 × 5 mL). The combined organic phases were dried (magnesium sulfate), filtered and concentrated under reduced pressure. The yellow oil thus obtained was subjected to column chromatography (silica, 1:3:6 v/v/v MeOH/ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.6) then gave *diquinane 25* (11 mg, 52%) as a clear, colourless oil (Found: $M^{+\cdot}$, 456.1606. $C_{25}H_{28}O_6S$ requires $M^{+\cdot}$, 456.1607). ^1H NMR (300 MHz, $CDCl_3$) δ 7.94–7.88 (complex m, 2H), 7.74–7.68 (complex m, 2H), 7.62–7.55 (complex m, 1H), 7.47–7.40 (complex m, 2H), 7.21–7.15 (complex m, 2H), 5.11 (m, 1H), 4.22 (dd, *J* = 11.1 and 3.4 Hz, 1H), 4.15 (dd, *J* = 11.1 and 4.6 Hz, 1H), 2.74–2.57 (complex m, 1H), 2.52 (ddd, *J* = 18.8, 8.8 and 1.2 Hz, 1H), 2.34 (s, 3H), 2.36–2.08 (complex m, 4H), 2.07 (dd, *J* = 18.8 and 4.8 Hz, 1H), 1.79 (dd, *J* = 12.9 and 8.0 Hz, 1H), 1.41 (dd, *J* = 12.9 and 11.1 Hz, 1H), 1.41–1.30 (complex m, 1H), 1.18 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 219.0 (C), 165.6 (C), 145.0 (C), 133.3 (CH), 132.3 (C), 129.8 (CH), 129.7 (CH), 129.4 (C), 128.4 (CH), 127.8 (CH), 74.3 (CH), 69.5 (CH_2), 52.4 (CH_2), 46.7 (CH), 46.3 (C), 44.2 (CH_2), 42.5 (CH_2), 39.7 (CH), 36.3 (CH_2), 27.7 (CH_3), 21.6 (CH_3); IR ν_{max} (KBr) 3020, 2954, 2918, 2848, 1736, 1727, 1452, 1364, 1269, 1216, 1190, 1177, 1110, 1097, 814, 756, 713, 667, 554 cm^{-1}; MS (EI, 70 eV) *m/z* 456 ($M^{+\cdot}$, <1%), 285 (11), 179 (21), 162 (25), 105 (100), 91 (34), 77 (32).

3.2.16. Compound 26

A solution of diquinane **24** (15 mg, 33 μmol) in THF/MeOH (0.6 mL of a 2:1 v/v mixture) was cooled to –78 °C then samarium diiodide (0.4 mL of a 0.1 M solution in THF, 40 μmol, 1.2 molar equiv.) was added dropwise over 0.25 h. The resulting mixture was stirred at –78 °C for 0.33 h then warmed to 0 °C, stirred at this temperature for 3 h then at 18 °C for 1 h. After this time, the reaction mixture was re-cooled to –78 °C and additional samarium diiodide (0.4 mL of a 0.1 M solution in THF, 40 μmol, 1.2 molar equiv.) was added dropwise over 0.03 h. The reaction mixture was stirred at –78 °C for 0.02 h and then allowed to warm to 18 °C. After 0.5 h at this temperature samarium diiodide (0.4 mL of a 0.1 M solution in THF, 40 μmol, 1.2 molar equiv.) was again added and after 0.5 h at 18 °C the reaction mixture was

quenched with potassium carbonate (1 mL of a saturated aqueous solution). The separated aqueous phase was extracted with diethyl ether (3 × 5 mL) then saturated with sodium chloride and extracted with dichloromethane (3 × 5 mL). The combined organic phases were dried (magnesium sulfate), filtered and concentrated under reduced pressure. The resulting yellow oil was subjected to column chromatography (silica, 1:3:6 v/v/v MeOH/ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.5) then gave *diquinane* ***26*** (3 mg, 21%) as a clear, colourless oil [Found: $(M+Na)^+$, 479.1500. $C_{25}H_{28}O_6S$ requires $(M+Na)^+$, 479.1504]. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93–7.89 (complex m, 2H), 7.73–7.69 (complex m, 2H), 7.61–7.56 (complex m, 1H), 7.46–7.42 (complex m, 2H), 7.20–7.16 (complex m, 2H), 5.12 (ddd, J = 7.8, 4.5 and 3.4 Hz, 1H), 4.21 (dd, J = 11.1 and 3.4 Hz, 1H), 4.17 (dd, J = 11.1 and 4.5 Hz, 1H), 2.62–2.72 (complex m, 1H), 2.53 (ddd, J = 19.0, 9.3 and 1.5 Hz, 1H), 2.34 (s, 3H), 2.34–2.14 (complex m, 4H), 2.05 (ddd, J = 19.0, 4.6 and 1.5 Hz, 1H), 1.84 (dd, J = 13.2 and 7.8 Hz, 1H), 1.58 (dd, J = 13.2 and 10.7 Hz, 1H), 1.22–1.14 (complex m, 1H), 1.18 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 219.0 (C), 165.6 (C), 145.0 (C), 133.4 (CH), 132.4 (C), 129.8 (CH), 129.7 (CH), 129.4 (C), 128.4 (CH), 127.9 (CH), 74.2 (CH), 69.5 (CH_2), 52.4 (CH_2), 46.7 (CH), 46.2 (C), 44.4 (CH_2), 42.4 (CH_2), 39.7 (CH), 36.3 (CH_2), 27.7 (CH_3), 21.6 (CH_3); IR ν_{max} (KBr) 2953, 1738, 1722, 1451, 1364, 1269, 1190, 1177, 1109, 1097, 1070, 1026, 976, 942, 815, 714, 667, 554 cm^{-1}; MS (ESI, +ve) *m/z* 495 [$(M+K)^+$, 7%], 479 [$(M+Na)^+$, 100], 455 (38), 285 (93), 206 (35), 163 (50), 135 (35), 105 (69).

3.2.17. Compound 29

A magnetically stirred solution of diquinane **25** (10 mg, 22 μmol) in THF (0.2 mL) was cooled to –78 °C then LiHMDS (26 μl of a 1 M solution in THF, 26 μmol, 1.2 molar equiv.) added dropwise. After 0.5 h the reaction mixture was warmed to 0 °C and then, after 1 h, to 18 °C. After 5 h at this temperature the reaction mixture was quenched with water (0.2 mL) and the separated aqueous phase washed with dichloromethane (5 × 1 mL). The combined organic layers were then dried (magnesium sulfate), filtered and concentrated under reduced pressure. The resulting light-yellow oil was subjected to column chromatography (silica, 1:3:6 v/v/v MeOH/ethyl acetate/hexane elution) and thereby affording two fractions, A and B.

Concentration of fraction A (R_f = 0.7) gave *compound* ***29*** (3 mg, 53% at 91% conversion) as a white, crystalline solid, mp = 128–133 °C (Found: $M^{+\bullet}$, 284.1412. $C_{18}H_{20}O_3$ requires $M^{+\bullet}$, 284.1412). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04–7.99 (complex m, 2H), 7.58–7.52 (complex m, 1H), 7.47–7.40 (complex m, 2H), 4.73 (t, J = 8.1 Hz, 1H), 2.56 (dd, J = 18.3 and 7.8 Hz, 1H), 2.46–2.17 (complex m, 4H), 2.10 (d, J = 9.1 Hz, 1H), 1.96 (d, J 12.3 Hz, 1H), 1.76 (dt, J = 13.7 and 9.1 Hz, 2H), 1.45 (dd, J = 12.3, 4.5 and 1.1 Hz, 1H), 1.26 (s, 3H), 1.19–1.11 (complex m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 222.6 (C), 165.8 (C), 132.9 (CH), 130.5 (C), 129.5 (CH), 128.3 (CH), 75.8 (CH), 50.9 (CH), 47.0 (C), 44.3 (CH_2), 43.1 (CH), 41.3 (CH), 38.4 (CH_2), 36.0 (CH_2), 25.8 (CH_2), 25.0 (CH_3); IR ν_{max} (KBr) 2930, 1732, 1717, 1451, 1336, 1313, 1275, 1258, 1179, 1143, 1112, 1068, 1024, 1003, 981, 710 cm^{-1}; MS (EI, 70 eV) *m/z* 284 [$M^{+\bullet}$, 3%], 163 (45), 162 (89), 134 (52), 106 (44), 105 (100), 93 (89), 92 (63), 77 (83). A sample of this material was recrystallised (ethyl acetate/hexane) to provide a crystal suitable for X-ray analysis. Details of this analysis are presented below and in Fig. 2.

Concentration of fraction B (R_f = 0.6) gave starting material **25** (1 mg, 9% recovery) as a clear, colourless oil that was identical, in all respects, with an authentic sample.

3.3. Single-crystal X-ray analysis of compounds 9 and 29

3.3.1. Data for Compound 9

$C_{14}H_{20}O_5$, M = 268.31, T = 200 K, monoclinic, space group $P2_1$, Z = 4, a = 14.7414(4), b = 6.6985(2), c = 15.2998(5) Å, β = 111.7498(19); V = 1403.23(8) Å^3, D_x = 1.270 g cm^{-3}, 2697 unique data ($2\theta_{max}$ = 50°), R = 0.0307 [for 2192 reflections with $I > 1.5\sigma(I)$]; Rw = 0.0376 (all data), S = 1.1764.

3.3.2. Data for Compound 29

$C_{18}H_{20}O_3$, M = 284.36, T = 200 K, monoclinic, space group $P2_1$, Z = 2, a = 6.8933(3), b = 7.4523(2), c = 14.8977(6) Å, β = 100.166(2); V = 753.29(5) Å^3, D_x = 1.254 g cm^{-3}, 1439 unique data ($2\theta_{max}$ = 50°), R = 0.035 [for 1084 reflections with $I > 2.0\sigma(I)$]; Rw = 0.081 (all data), S = 0.82.

3.3.3. Structure Determination

Images were measured on a Nonius Kappa CCD diffractometer (MoKα, graphite monochromator, λ = 0.71073 Å) and data extracted using the DENZO package.[35] Structure solution was by direct methods (SIR92).[36] The structures of compounds **9** and **29** were refined using the CRYSTALS program package.[37] Crystallographic data (excluding structure factors) have been deposited at the Cambridge Crystallographic Data Centre (CCDC nos. 763134 and 760492 for compounds **9** and **29**, respectively). These data can be obtained free-of-charge *via* www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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